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GELATIN SPONGE

SURGICAL INVESTIGATION OF A NEW MATRIX USED IN CONJUNCTION WITH THROMBIN IN HEMOSTASIS

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The control of vascular ooze has proved to be one of the most baffling problems in neurosurgery. Completely inappropriate for the ligature and equally outside the scope of the Cushing clip or the electrocautery, this type of hemorrhage responds to some extent to styptics, to pressure and to hot water, but all too frequent failures of these methods are attested by the guard under which patients must be kept after intracranial and intraspinal operations in order to signal the need of reexploration for removal of clot. To the problem of ooze must be added that of the bleeding of small vessels, especially arteries, when their destruction is likely to damage neighboring structures, and the bleeding from important veins whose function must be maintained following hemostasis.

Time and again the neurosurgeon has turned to the biochemist for an answer to these puzzles.[1] The search has concerned the diversion of one or more of the elements involved in the clotting cycle to the end that clotting, forced at the site of bleeding, might become usefully hemostatic. Recent successes emphasize the importance of this search, and the technic of hemostasis represented by the use of strong clotting agents applied directly or with the aid of an absorbable carrier promises to bring much of this problem under control. To understand the technic one must be familiar with the clotting cycle.

THE CLOTTING CYCLE

Five substances are involved in the mechanism of blood clotting. These are thought of as factors in a classic pair of equations:

Prothrombin + Ca^{++} + thromboplastin = thrombin (1)

Thrombin + fibrinogen = fibrin (2)

Prothrombin is a constituent of the plasma, and its supply is dependent on a normally functioning liver and an ample amount of vitamin K. Calcium, indispensable to the cycle, is significantly altered in amount in few disease conditions. Fibrinogen, a plasma protein, while present in very small amounts (300 to 600 mg. per hundred cubic centimeters), is, however, greatly in excess of the amounts actually needed. It is rarely altered and in general can be depended on to fulfil its function of completing the reaction by combining with thrombin to form fibrin, provided the other factors are furnished. These three, prothrombin, calcium and fibrinogen, have not emerged as substances practicable for surgical hemostasis.

The two remaining factors of the clotting reaction, thromboplastin and thrombin, have met with notable success. The earlier neurosurgeons who used bits of muscle or the phospholipid cephalin to control bleeding were, in reality, invoking the clotting activity of thromboplastin, for thromboplastin exists in tissue cells as well as in the platelets of the blood. The brain and lungs carry the largest amounts, but other tissues have their share. The use of tissue thromboplastin reduces the clotting time of blood from its normal span of five to eight minutes to a matter of twelve to twenty seconds. This reaction is the basis of the tests used currently for the study of the prothrombin time.

THROMBIN AS A HEMOSTATIC AGENT

Thrombin has proved to be the most powerful of all clotting agents, since it combines with soluble fibrinogen in a virtually instantaneous reaction to precipitate the crystalline fibrin of the blood clot. The use of thrombin in surgical practice, howeyer, was dependent on two developments which have only recently been achieved: the extraction of the active principle in adequate potency and the bacteriologic sterility of the product.

The existence of thrombin was made known by Schmidt in the 1890's, but preparations of useful potency were first introduced in 1933, by Mellanby.[2] Seegers and his associates at the University of Iowa bettered this preparation

This substance will soon be made available by the Upjohn Company under the name "Gelfoam."

1. Light, R. U.: Hemostasis in Neurosurgery, J. Neurosurg. **2**:414-434, 1945.

2. Mellanby, J.: Thrombase: Its Preparation and Properties, Proc. Roy. Soc., London, s.B **113**:93-106, 1933.

substantially,[3] yet the material was not aseptic and could be employed only on exposed or drained wounds, such as the wound of a mastoidectomy, the donor areas of skin grafts and the bleeding tooth sockets of persons with hemophilia.[4] Dramatic results in these fields led to further purification and to methods of sterilization, and in 1943 a highly concentrated aseptic beef thrombin was marketed[5] for use in surgical hemostasis. The material was nontoxic (6,000 units was injected into a rat without ill effect), and clinical experience based on 225 surgical cases was reported.[6] In these cases the thrombin was applied as a spray or a dry powder sprinkled on. Blood clotted on contact, but the clot did not always prove to be hemostatic, since it was apt to be dislodged by the aftercoming flow. Several important observations were made: 1. Thrombin is compatible with the sulfonamide drugs. 2. Local irritation is absent. 3. Repeated use does not cause sensitization. 4. Intravascular thrombus formation does not result from its use.

Meanwhile, rabbit thrombin had been produced and found useful on small experimental human wounds.[7]

In 1941 there began the study of the fractionation of human blood, following the suggestion of Cohn[8] that human serum albumin should be valuable in the treatment of shock, and in the course of the later large scale production of serum albumin for the armed forces, both thrombin and fibrin were secured as by-products. The human thrombin, though of relatively low potency, proved clinically useful in hemostasis in connection with a fibrin carrier.[9]

Clinical experiences therefore confirmed the proposition declared by Quick,[10] that the clotting activity of thrombin follows group rather than species orientation and that the thrombins of mammals appear to be identical, although they differ from those of birds and of amphibians. The antigenicity of thrombin has not been fully evolved, but it is altogether possible that in antigenicity, too, it will prove to be unrelated to species and that, as with insulin, an animal can be sensitized to thrombin from any species, including its own.

ABSORBABLE CARRIERS OF THROMBIN

The problem of keeping the thrombin intimately in contact with a bleeding orifice until a solid adhesive clot forms was anticipated in part by experimental work done thirty years ago, when Cushing[11] suggested that "whipped clot" might be used to plaster on bleeding surfaces just as he then employed solidified blood clots, thus projecting an elementary form of the absorbable patch. Under his direction, Grey (1915)[12] used washed, sterilized human and sheep fibrin, and in 1916 Harvey,[13] working again with fibrin, called attention to the clotting activity of cephalin and the Kocher-Fonio coagulen and complained that these had to be applied with "some form of tampon in the removal of which the clots were dragged from the hemorrhagic areas." He was close to the present solution of the problem. These studies showed that fibrin was relatively nonirritating to tissues—less so than a muscle implant, for example—and that it was absorbed satisfactorily.

Recently, fibrin was restudied as an absorbable matrix, and three other absorbable substances were introduced:

1. *Fibrin Foam.*—In 1944, Ingraham and Bailey[14] reported on the use of a matrix of fibrin

3. Seegers, W. H.; Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: The Purification of Thrombin, J. Biol. Chem. **126**:91-95, 1938.

4. Seegers, W. H.; Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: The Use of Purified Thrombin as an Hemostatic Agent, Science **89**:86, 1939.

5. By Parke, Davis & Company.

6. Tidrick, R. T.; Seegers, W. H., and Warner, E. D.: Clinical Experience with Thrombin as a Hemostatic Agent, Surgery **14**:191-196, 1943. Tidrick, R. B., and Warner, E. D.: Fibrin Fixation of Skin Transplants, ibid. **15**:90-95, 1944.

7. Lozner, E. L.; MacDonald, H.; Finland, H., and Taylor, F. H. L.: The Use of Rabbit Thrombin as a Local Hemostatic, Am. J. M. Sc. **202**:593-598, 1941.

8. Cohn, E. J.: The Properties and Functions of the Plasma Proteins, with a Consideration of the Methods for Their Separation and Purification, Chem. Rev. **28**:395-417, 1941.

9. Edsall, J. T.; Ferry, R. M., and Armstrong, S. H., Jr.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: XV. The Proteins Concerned in the Blood Coagulation Mechanism, J. Clin. Investigation **23**:557-563, 1944.

10. Quick, A. J.: Qualitative Differences in the Prothrombin, Thromboplastin and Thrombin in Different Species, J. Biol. Chem. **120**:xcix, 1938.

11. Cushing, H.: The Control of Bleeding in Operations for Brain Tumors, with the Description of Silver "Clips" for the Occlusion of Vessels Inaccessible to the Ligature, Tr. Am. S. A. **29**:389-410, 1911.

12. Grey, E. G.: Fibrin as a Hemostatic in Cerebral Surgery, Surg., Gynec. & Obst. **21**:452-454, 1915.

13. Harvey, S. C.: The Use of Fibrin Paper and Forms in Cerebral Surgery, Boston M. & S. J. **174**: 658-659, 1916; Fibrin Paper as an Hemostatic Agent, Ann. Surg. **68**:66-70, 1918.

14. Ingraham, F. D., and Bailey, O. T.: The Use of Products Prepared from Human Fibrinogen and Human Thrombin in Neurosurgery: Fibrin Foams as Hemostatic Agents; Fibrin Films in Repair of Dural Defects and in Prevention of Meningocerebral Adhesions, J. Neurosurg. **1**:23-44, 1944. Ingraham,

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prepared by E. A. Bering Jr.,[15] made spongy and porous and called fibrin foam. In use it was soaked in thrombin, squeezed out and laid on the bleeding surface. The texture of the material presented a meshwork in which clot could form, and the sponginess aided by drawing blood into the meshes.

This material was studied on monkeys and on 95 patients. It was found to have a speedy and reliable hemostatic effect and to be absorbed by the tissues with but minimal reaction. The substance was made available to the armed forces, and a recent report by Woodhall[16] recounts its satisfactory use in 226 operations in rehabilitation neurosurgery.

2. *Oxidized Cellulose.*—The conversion of cellulose (surgical cotton or gauze) to an organic acid by the action of nitrogen dioxide renders that material soluble at the alkalinity present in tissue juices and absorbable by the body.[17] It was employed by Putnam[18] as a carrier for thrombin, but the recent disclosure of Seegers and Doub[19] that thrombin is inactivated by the acidity of oxidized cellulose (about p_H 4) invalidates his results. The acidity can be neutralized with 1 per cent sodium bicarbonate and the material is then harmless to the clotting agent.[20] In general, however, oxidized cellulose should be classed as an absorbable pack rather than as a thrombin carrier, and it possesses, perhaps fortunately, a slight stypticity helpful in prevention of ooze.

3. *Starch Sponge.*[21]—This substance is nonirritating and readily absorbable, but the samples so far available have been found friable and impractical for use in surgical practice.

4. *Gelatin Sponge.*—The recent announcement by Correll and Wise[22] of the successful production of an absorbable, spongelike matrix derived from gelatin relieves the precarious dependency on human blood as the source of the foam type of thrombin carrier. Gelatin, like fibrin foam, is a protein but with the important distinction of being a nonspecific, "universal" protein devoid of antigenicity and therefore procurable from any animal. Beef is the common source. Because gelatin is a soluble substance, the problem was to convert it from a soluble to an insoluble but absorbable material. By succeeding at the same time in foaming it into an efficient sponge, which can be wetted, wrung out and refilled indefinitely, the special physical properties which gave success to fibrin foam as a thrombin carrier have been duplicated. Gelatin sponge is, in fact, more efficient. A cubic centimeter weighs only 9 mg., yet it will absorb nearly 0.5 Gm. (forty-five times its weight) of water or blood (fig. 2). It is free from the friability of fibrin foam, can be cut with a scalpel without disintegration and is obtainable from the

Fig. 1.—Specimens of gelatin sponge.

F. D.; Bailey, O. T., and Nulsen, F. E.: Studies on Fibrin Foam as a Hemostatic Agent in Neurosurgery, with Special Reference to Its Comparison with Muscle, ibid. **1**:171-181, 1944. Bailey, O. T., and Ingraham, F. D.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: XXI. The Use of Fibrin Foam as a Hemostatic Agent in Neurosurgery; Clinical and Pathological Studies, J. Clin. Investigation **23**:591-596, 1944. Ingraham, F. D., and Bailey, O. T.: Clinical Use of Products of Human Plasma Fractionation: III. The Use of Products of Fibrinogen and Thrombin in Surgery, J. A. M. A. **126**:680-685 (Nov. 11) 1944.

15. Bering, E. A., Jr.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: XX. The Development of Fibrin Foam as a Hemostatic Agent and for Use in Conjunction with Human Thrombin, J. Clin. Investigation **23**:586-590, 1944.

16. Woodhall, B.: Fibrin Foam as a Hemostatic Agent in Rehabilitation Neurosurgery, J. A. M. A. **126**:469-471 (Oct. 21) 1944.

17. Yackel, E. C., and Kenyon, W. O.: The Oxidation of Cellulose by Nitrogen Dioxide, J. Am. Chem. Soc. **64**:121-127, 1942. Unruh, C. C., and Kenyon, W. O.: Investigation of the Properties of Cellulose Oxidized by Nitrogen Dioxide, ibid. **64**:127-131, 1942.

18. Putnam, T. J.: The Use of Thrombin on Soluble Cellulose in Neurosurgery: Clinical Application, Ann. Surg. **118**:127-129, 1943.

19. Seegers, W. H., and Doub, L.: Oxidized Cellulose and Thrombin, Proc. Soc. Exper. Biol. & Med. **56**:72-73, 1944.

20. Uihlein, A.; Clagett, O. T., and Osterberg, A. E.: The Use of Oxidized Cellulose for Hemostasis in Surgical Procedures: Preliminary Report, Proc. Staff Meet., Mayo Clin. **20**:29-32, 1945. Seegers and Doub.[19]

21. Bice, C. W.; MacMasters, M. M., and Hilbert, G. E.: Proposed Use of Starch Sponges as Internal Surgical Dressings Absorbable by Body, Science **100**: 227-228, 1944.

22. Correll, J. T., and Wise, E. C.: Certain Properties of a New Physiologically Absorbable Sponge, Proc. Soc. Exper. Biol. & Med. **58**:233-235, 1945.

manufacturer in pieces of any size or shape (fig. 1). When wet, it clings to the contours of the surface to which it is applied.

Comparative studies of this substance and fibrin foam [22] have shown that both are digested in about thirty minutes in standard trypsin and

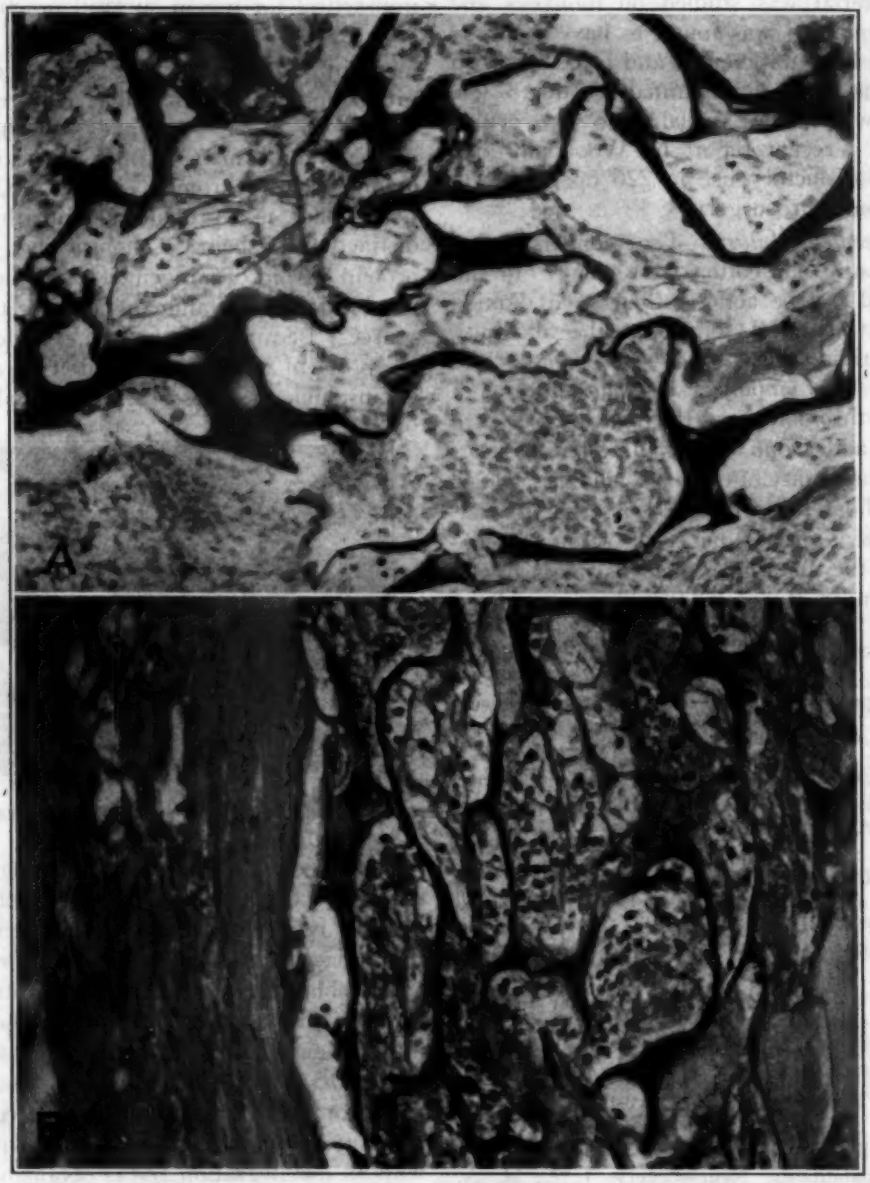

Fig. 2.—*A*, the microscopic appearance of gelatin sponge after clot has formed in its meshes. *B*, gelatin sponge on dura, used to repair a torn venous sinus, from a specimen taken three days after surgical implantation. Note absence of cellular reaction. In this and succeeding illustrations, the tissue, either dura or brain, is placed at the left and the gelatin sponge at the right.

that nodules implanted in rat muscle disappear in about thirty days in the case of the gelatin sponge and in about fifty days in the case of fibrin foam, the local tissue reactions being slight and about equal in degree.

SURGICAL INVESTIGATION OF GELATIN SPONGE

1. *Animal Experiments.*[23]—We conducted an investigation of gelatin sponge as a thrombin carrier by means of a graduated survival study in Macacus rhesus monkeys, in which 67 cranial operations were performed on 56 animals, to

23. The animals utilized in this study were provided by The Upjohn Company. The bovine thrombin and the gelatin sponge constituted Upjohn research preparations. The fibrin foam and the human thrombin were prepared by The Upjohn Company in collabora-

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consider the following problems: the hemostatic effectiveness of the substance, the tissue reaction to its presence and the rate of its absorption and, finally, a comparison of these factors with those of fibrin foam simultaneously implanted in comparable areas in the same animals. The antigenicity of bovine thrombin was also considered.

In the first experiment 36 animals were used. Operations were performed with sterile surgical technic and general anesthesia. Pieces of gelatin sponge and of fibrin foam, cut 4 by 6 by 10 mm., soaked in bovine thrombin 300 units (Upjohn) per cubic centimeter,[24] were implanted; the wounds were closed and the animals permitted to survive according to the following schedule in days: three, six, twelve, twenty, thirty, forty-five and sixty, 1 animal being kept to one hundred and twenty days. Five types of implantations were made: (*a*) to repair a torn venous sinus, (*b*) on the surface of intact brain, (*c*) on bleeding brain, (*d*) by insertion into the recess left by excision of a block of cortex and (*e*) by insertion deep in the brain. Two other experiments were done on similar lines but with variations. Four animals, prepared as in *a, b, c* and *d,* were reoperated on to repeat the implantations after an interval of four months and were then killed after a further interval of thirty days. Ten animals, prepared as in *a* and *e* but with substitution of human thrombin for bovine thrombin, were killed according to the schedule previously listed from three to thirty days.

Histologic Studies: Observations showed that there was no appreciable difference between the tissue reactions to fibrin foam and to gelatin sponge when these matrices were implanted under comparable conditions. Up to three days, each material was surrounded by and filled with blood and provoked no tissue reaction (fig. 2). By the sixth day, cellular reaction began (fig. 3*A*). The maximum reaction occurred about the twelfth day. In subdural implants, the material tended as a rule to separate from the brain and become attached to the dura, in which there arose a definite cellular response consisting of lymphocytes and huge giant cells. Even when separation from the brain did not occur at this time, no cellular reaction was found in the brain tissue (fig. 3*B*). By the twentieth day the material was breaking up in the subdural implants. The dura continued to show lymphocytic and giant cell reaction, while the brain surface showed no appreciable reaction (fig. 4*A*). With implants deep in brain tissue, there remained at the thirtieth day thinned-out, broken fibers of material with some phagocytic, lymphocytic and giant cell reaction (fig. 4*B*). After the thirtieth day the reaction on dura and uninjured brain surface was negligible. In severely injured brain, phagocytes and giant cells remained in appreciable numbers up to forty-five days. The ultimate glial reaction was no more, however, than would be expected from the injury alone.

When implants were repeated after intervals of one hundred and nineteen to one hundred and thirty-nine days, the tissues, examined thirty days after the last operation, showed no appreciable difference in reaction from that seen after single implants. When fibrin foam and gelatin sponge prepared with human thrombin were implanted on dura and in subcortical areas of the brain, there was no difference in reaction from that seen when bovine thrombin was used.

An important disclosure was the absence of intravascular clotting (thrombus formation) when thrombin-soaked matrices were employed to patch openings in veins. At 27 operations, performed on 18 animals, the superior sagittal sinus was opened and repaired with a thrombin-soaked matrix on forty-one occasions, including the coincidental implants of gelatin sponge and fibrin foam. In several of these animals, the sinus was reopened at 2 or 3 successive operations. In no single instance was there evidence that clotting had extended into the venous channel, nor was there any evidence that the patch had been defective in hemostasis.

Antigenicity of Bovine Thrombin: In order to study the antigenicity of bovine thrombin, we planned an experiment using thrombin in a manner simulating its actual surgical use, that is, as a hemostatic agent on bleeding surfaces, deliberately omitting the additional introduction of the substance by intramuscular or intravenous routes. To favor sensitization, however, a high concentration of thrombin (1,500 units per cubic centimeter) was chosen, although it was recognized that optimum hemostasis with the matrix

tion with Dr. Edwin J. Cohn, of the Department of Physical Chemistry and the Plasma Fractionation Laboratory, Harvard Medical School, from blood collected by the American Red Cross, under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. The fibrin foam used came from jars sorted out from a regular production lot because of minor imperfections.

24. It is unfortunate that biochemists have not yet adopted a standard unit of potency for thrombin. The Upjohn unit[22] is defined thus: If 0.1 cc. of a thrombin solution clots 0.5 cc. of a specially oxalated bovine plasma in fifteen seconds, that solution is considered to have a potency of 30 units per cubic centimeter. Roughly compared, the Upjohn unit has one third the potency of the Iowa unit. Throughout the remainder of the paper the Upjohn unit is implied.

method is obtained with dilutions of about 100 units per cubic centimeter.

Five animals were subjected to multiple operations at intervals of three days, some going through 2 and some 3 operations, followed after an interval by an attempt to produce anaphylaxis by injection of bovine thrombin directly into the brain. The injections to produce shock were done on the fifteenth day following the last operation for 2 animals and on the twenty-fourth, thirty-second and forty-fifth days for the others. The animals were killed three days later. As an additional clue in the search for hypersensitization, serum was taken for precipitin tests against the antigen (bovine thrombin) on three occasions: on the day of the last operation, on the day of injection and at the time the animals were killed.

The results of these studies were uniformly negative. All precipitin reactions were normal; there was neither neurologic nor general disturbance following the intracerebral injection, and the areas of injection failed to show evidence of the local necrosis or inflammation associated with the Arthus phenomenon.

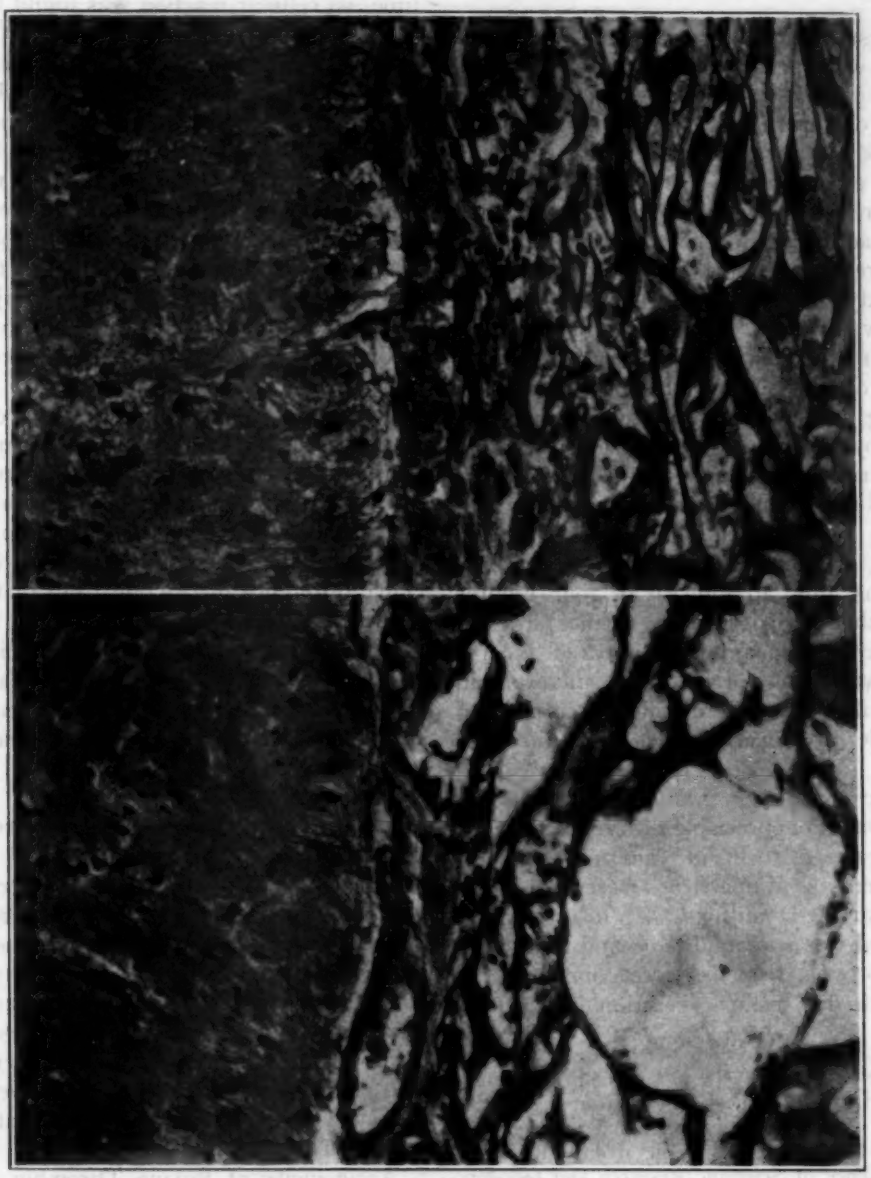

Fig. 3.—*A*, gelatin sponge at six days on surface of brain which has been injured by needle pricks. Note absence of reaction in brain. *B*, gelatin sponge twelve days after implanting on surface of normal brain. There is no cellular reaction in brain. (Lymphocytic and giant cell reaction was present in meninges.)

2. *Clinical Experiences.*—Our clinical experiences were gained in the course of twenty-four routine neurosurgical procedures, which in-

cluded operations for brain tumor, subtemporal decompression, elevation of depressed skull fracture, scalenotomy, ligation of the carotid artery and laminectomy. The material was found exceptionally efficient and reliable in controlling the types of bleeding for which the patch technic is suitable, and it afforded easier handling, wider contributions they have rendered to the new technic.

Method of Using Gelatin Sponge: The control of bleeding by the use of gelatin sponge soaked with thrombin may be compared to repairing a tire by the use of a rubber patch and a vulcanizing substance. Gelatin sponge is the

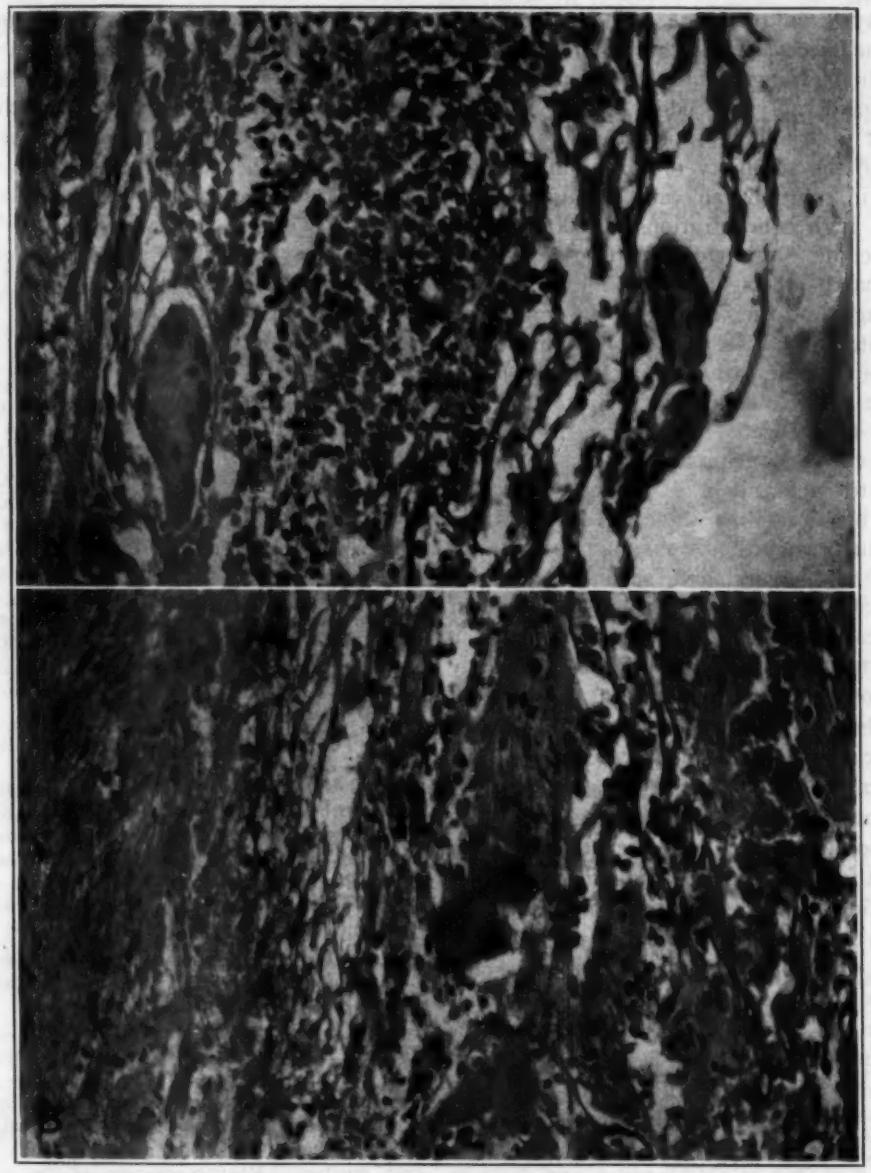

Fig. 4.—*A*, gelatin sponge twenty days after implantation on injured brain, showing lymphocytic and giant cell reaction and breaking up of material. *B*, gelatin sponge thirty days after being embedded in brain. Material is disappearing, and there is lymphocytic and giant cell reaction.

latitude of application and fewer failures than did fibrin foam. Fundamentally, however, fibrin foam and gelatin sponge serve the same purposes, and the extensive experiences with fibrin foam reported by Ingraham and Bailey and by Woodhall should be consulted for the important patch and thrombin the vulcanizer. Whereas, however, the tire patch itself is impervious, the gelatin has been foamed—for a special reason—into a porous sponge and becomes an impervious seal only after blood flows into the meshes, mixes with thrombin and clots.

The sponge is the mixing chamber. The thickness of the sponge determines the depth of the clot. A thin sponge is adequate for minor ooze; a thicker one is required to stem a copious flow. In general, and for most purposes, we believe that a sheet of sponge 4 to 6 mm. thick is correct. If the flow is so heavy that blood seeps through the meshes, a thicker piece should be used, say 8 mm. or more. The areal dimensions of the piece are determined solely by the extent of the bleeding surface. The patch should overlap considerably the edges of the bleeding orifice if it is to adhere satisfactorily.

Owing to the solubility of thrombin, its concentration in solution can vary through a wide range. At high concentrations (1,000 units or more per cubic centimeter) clotting activity is so great that blood is halted on the under side of the sponge, and the center and the upper side remain white and unused. It is our opinion that the thrombin concentration, as well as the thickness of the sponge, should be adjusted to permit blood to saturate the matrix thoroughly before the clot is precipitated, and if thrombin is diluted to yield about 100 units per cubic centimeter blood clots satisfactorily in the thickness previously suggested. As supplied, thrombin is a sterile powder, and, since each ampule contains 1,500 units, the addition of 15 cc. of water gives the recommended concentration. This amount, incidentally, is sufficient ordinarily for a neurosurgical operation.

The method of handling the sponge is important. It is cut in the dry state to the desired size with the scalpel. The surgical nurse then wets the material thoroughly by dipping it in the thrombin solution (for convenience kept in a shallow Petri dish) and kneading forcefully between the fingers until the air is completely expelled from the meshes and the material becomes like a limp rag. After reimmersion in the solution, it unrolls and swells to the original shape. The surgeon has two choices. He may pick out a piece dripping with thrombin, lay it on the bleeding area, press it in place with a cotton pledget and remove the excess thrombin by suction applied through the pledget. After release of pressure, blood flows into the matrix, combines with thrombin and clots. The cotton can be loosened with a drop or two of water and peeled away. As an alternative, the sponge may be blotted of its excess thrombin on a towel before application. Momentary pressure through a cotton pledget is helpful in seating the patch, and the sucker is useful in obtaining a dry field. Secure hemostasis is obtained in about ten to fifteen seconds.

The adhesive strength of the patch has not been measured experimentally. Practice has shown that it withstands venous pressure, possibly without regard to the size of the vein, and that small arteries may be held successfully. In general, however, the method is inappropriate for arterial hemostasis and should be reserved for ooze and venous bleeding. Pieces are not easily knocked loose, although if caught by the sucker they disappear. If a piece is dislodged, there is little likelihood that it can be made to stick again, and a new one should be applied. Adhesion depends on the crystallization of fibrin, aided probably by the gluelike property of blood platelets.

REPORT OF CASES

CASE 1.—*Débridement and elevation of severe compound depressed skull fracture; repair of multiple tears in superior sagittal sinus with gelatin sponge; tight closure; recovery.*

W. M. V., an automobile finance agent, aged 32, drove his car at high speed into a tree. Operation was performed within an hour of the injury. His face and forehead were caved in, and the torn brain lay exposed through a long scalp laceration. Copious washings were given from an irrigation can, followed by removal and sacrifice of several plates of frontal bone. The scalp was closed tightly without drain. Sulfonamide compounds and penicillin were administered for a week afterward although not applied topically. Rhinorrhea persisted for eight days and then ceased spontaneously. The wound healed by first intention, and the patient left the hospital two weeks after the accident. Four months later he was working steadily. Petit mal attacks had begun.

The availability of the hemostatic patch was an important factor in this man's recovery. The superior sagittal sinus was bleeding from several tears, especially from a hidden opening beneath the unfractured cranium. Both the exposed and the hidden tears were repaired by use of strips of sponge measuring about 8 by 20 mm., cut from sheets in the supply bottle which averaged about 3 mm. thick. Bovine thrombin, 100 units per cubic centimeter, was used.

CASE 2.—*Occipital craniectomy for biopsy; tearing of lateral sinus; repair of sinus with gelatin sponge; postmortem examination.*

A. W., a druggist, aged 59, sustained a blow to the head in June 1944, and eight weeks later severe headache developed, followed by staggering gait, slurred speech, urinary incontinence, failing vision and mental disorientation. He arrived at the hospital unconscious. No one knew of this history, which was learned only post mortem. Roentgenograms of the skull revealed a destructive lesion of the bone near the central portion of the right lambdoidal suture, and the roentgenologist advised preliminary biopsy before considering further surgical treatment. This was done. The patient died three days later. Autopsy revealed an extremely large subdural hematoma on the left side.

The operation was done by turning down a small occipital scalp flap to expose the soft punched-out area of bone. This was removed by drilling four holes through the neighboring sound bone, joining these with cuts with the channel rongeurs and dissecting the block upward from the dura. It lay directly above

the transverse sinus, which was torn during the removal. Bleeding was free. It was controlled by the application of a piece of gelatin sponge, cut about 4 by 6 by 15 mm., soaked in bovine thrombin, 300 units per cubic centimeter. An oozing area on the dura was likewise readily controlled. At autopsy the sinus was found to be patent, without evidence of thrombus formation. (This was true also in the case of a patient with brain tumor, dying on the eighth day after operation, in which the superior sagittal sinus had been repaired by gelatin sponge [fig. 5]).

CASE 3.—*Removal of herniated intervertebral disk at the fifth lumbar interspace; use of gelatin sponge to control venous bleeding and to seal a leak of spinal fluid.*

D. M. K., a housewife aged 29, had suffered repeated attacks of sciatica on the right side for thirteen years. The first attack began when she awoke from anesthesia after an appendectomy. Another one coincided with a pregnancy. For the past year she had suffered pain and numbness in the back of the right hip, the side of the thigh and the foot, which was thought typical of a herniated lumbar intervertebral disk. Neurologic examination pointed to the fifth lumbar interspace, and roentgenograms showed reduction of that space. With the patient under spinal anesthesia, operation was performed through an interlaminal approach to the interspace, and a large fully extruded nucleus pulposus was removed. The fourth interspace was similarly exposed, but there the disk proved normal. The patient was discharged nine days later. She had been free from pain for six months.

Gelatin sponge soaked in bovine thrombin, 100 units per cubic centimeter, was used to control the bleeding of the spinal epidural veins at both interspaces. Pieces 10 to 12 mm. long by 6 to 10 mm. wide were implanted, with good effect. At the fourth interspace the dura was nicked, and spinal fluid flooded the recess. This opening was readily sealed by applying a piece of thrombin-soaked sponge, which was first smeared with blood.

Fig. 5.—Gelatin sponge from dura of a patient who died on eighth postoperative day. Clot is still present in meshes, and cellular reaction is minimal.

ANTIGENICITY STUDIES

Precipitin tests (bovine thrombin in dilutions from 1 to 10 to 1 to 100,000, layered above blood serum) were done on 15 patients at intervals of from ten to one hundred and ninety-four days after operations in which bovine thrombin was employed for surgical hemostasis, and the results were negative without exception.

CONCLUSIONS

Gelatin sponge is an efficient matrix for use in conjunction with thrombin in the "patch technic" of surgical hemostasis.

The successful use of the patch technic is dependent on certain principles, which are discussed in detail. Histologic studies show that gelatin sponge when implanted on bleeding dura, on uninjured brain and on injured brain provokes a predictable, mild cellular reaction and is absorbed in twenty to forty-five days without leaving residual reaction.

The repair of venous sinuses with gelatin sponge leaves the lumen of the vein patent and without evidence of thrombus formation.

The use of bovine thrombin in the amounts required for surgical hemostasis in human beings appears to be free from the danger of antigenicity.

The "patch technic" of hemostasis is no longer dependent on human blood for its materials.

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SKIN BACTERIA

THEIR ROLE IN CONTAMINATION AND INFECTION OF WOUNDS

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There are seven main sources of contamination of clean operative wounds, namely, instruments, drapes, hands of operating personnel, droplet infection from nose and throat, suture material, air-borne bacteria and organisms in the skin. Hart,[1] Meleney,[2] Weaver,[3] Dandy[4] and many others have carried out investigations to prove the existence of these sources of contamination and have devised methods of combating all of them with the exception of bacteria of the skin. In a previous publication,[5] it has been shown that most of the transient organisms of the skin are superficial and can be removed by mechanical and chemical cleansing. The resident bacteria are situated so deep in the hair follicles and sebaceous glands that they cannot be removed by mechanical means without injury to the skin. The antiseptics generally used do not penetrate sufficiently to reach the organisms located in the deeper parts of these structures. Although the surface of the skin may be rendered relatively free of bacteria by mechanical and chemical cleansing before operation, during operation the resident bacteria rise to the surface and multiply and thus constitute an important source of contamination. The purposes of the investigations reported here are to determine the type and number of bacteria of the skin gaining entrance to the wound during the course of routine operations and their role in the infection of wounds.

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2. Meleney, F. L.: Infection in Clean Wounds, Surg., Gynec. & Obst. **60**:264-276, 1935.

3. Weaver, G. H.: Droplet Infection and Its Prevention by Face Mask, J. Infect. Dis. **24**:218-230, 1919.

4. Dandy, W. E.: The Importance of More Adequate Sterilization Processes in Hospitals, Bull. Am. Coll. Surgeons **16**:11-12, 1932.

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EXPERIMENTS

To determine the number and type of organisms gaining entrance to the wounds during operations, cultures were taken as follows:

1. For preoperative preparation, the surface of the skin was washed with green soap and water, followed by 70 per cent alcohol and ether. Just before operation, two layers of 3.5 per cent solution of iodine were applied and then removed with 70 per cent alcohol. After the surface became dry, a sterile sponge, thoroughly moistened with isotonic solution of sodium chloride, was rubbed over the skin. The saline solution was then expressed from the sponge into a sterile container. All this solution was cultured by the pour plate method. After twenty-four hours of incubation, the number and type of colonies present were recorded.

2. Immediately after the incision in the skin had been made, towels were clipped to the edges to prevent, so far as possible, surface bacteria from getting into the wound. The wound was then irrigated with a small amount of isotonic solution of sodium chloride and the solution cultured by the method previously mentioned.

3. After the primary object of the operation had been accomplished, the wound was again irrigated and the solution cultured as in paragraph 2.

4. After the wound had been closed, the towels were removed, and the final culture was made from the surface of the skin, as described in paragraph 1.

Although there is no accurate method of recovering all the organisms in the wound or on the surface of the skin, the procedures used gave uniform results, which were satisfactory for comparison. All operations were performed under bactericidal radiant energy to minimize contamination from the air.

RESULTS

Cultures were taken during thirty-five operations for inguinal hernia. Data from 10 of the cases are listed in table 1 and represent the average results in this series. Two operative teams were working simultaneously during the bilateral operations; therefore, the time factor was not significant. Cultures were taken during one hundred and fifteen operations of other types, and the results in 10 average cases are listed in table 2.

It is noted in table 1 that a few organisms were obtained from the surface of the skin immediately after mechanical and chemical cleansing. Some of the cultures were sterile, but of those which grew organisms the greater number

grew Staphylococcus albus. Other bacteria, including Staphylococcus aureus and Escherichia coli, and a nonpathogenic fungus were present occasionally in small numbers.

The number of organisms obtained from the wound just before closure was considerably greater than the numbers recovered in the first two cultures. This is probably due to the fact that the bacteria which gained entrance to the wound multiplied during the time of operation. Some of them possibly gained entrance to the wound in perspiration flowing over the skin edges, regardless of the fact that towels were closely applied. These bacteria also belong to the resident flora and are relatively nonpathogenic.

In the second culture, it is shown that in most instances a few organisms are carried into the wound with the skin knife. They are of the same variety as those obtained from the surface of the skin, are relatively nonpathogenic and belong to the resident flora.

TABLE 1.—*Results of Culture in Cases of Inguinal Herniorrhapy*

Operation	Culture of Skin Before Incision, Number and Type of Colonies	Culture of Wound After Incision in Skin, Number and Type of Colonies	Culture of Wound Before Closure, Number and Type of Colonies	Culture of Skin After Operation, Number and Type of Colonies
1	Left: no growth	1 Staph. albus	1 B. subtilis	164 Staph. albus
	Right: 1 fungus; 14 Staph. albus	No growth	9 Staph. albus	266 Staph. albus; 1 fungus
2	No growth	No growth	2 Staph. aureus; 1 Staph. albus	70 Staph. albus
3	2 Staph. albus	2 B. subtilis; 1 Staph. citreus	1 B. subtilis	Uncountable Staph. albus
4	Right: 2 Staph. albus	36 Staph. albus	100 Staph. albus	Uncountable Staph. albus and citreus
	Left: 43 Staph. albus; 2 Staph. aureus	4 Staph. albus	21 Staph. albus	Uncountable Staph. albus and citreus
5	2 E. coli	No growth	12 Staph. albus; 2 E. coli	Uncountable Staph. albus
6	Right: no growth	2 Staph. albus	26 Staph. albus	Uncountable Staph. aureus and albus
	Left: no growth	3 Staph. albus	400 Staph. albus; 50 sarcina	Uncountable Staph. aureus and albus
7	Right: 1 Staph. albus	No growth	No growth	Uncountable Staph. albus and citreus; 100 E. coli
	Left: 1 fungus	No growth	400 Staph. albus and citreus	Uncountable Staph. albus and alpha; streptococci
8	No growth	20 Staph. albus	8 Staph. aureus; 105 Staph. albus	Uncountable Staph. albus and E. coli
9	No growth	No growth	No growth	4 Staph. albus; 1 fungus
10	1 sarcina	2 Staph. albus; 1 fungus	25 Staph. albus	Uncountable Staph. albus

TABLE 2.—*Results of Culture in Miscellaneous Operations*

Operation	Culture of Skin Before Incision, Number and Type of Colonies	Culture of Wound After Incision in Skin, Number and Type of Colonies	Culture of Wound Before Closure, Number and Type of Colonies	Culture of Skin After Operation, Number and Type of Colonies
1. Cholecystectomy and appendectomy	2 Staph. albus	No growth	Uncountable E. coli	20 Staph. albus; 5 E. coli
2. Radical mastectomy	25 Staph. albus; 6 Staph. aureus	No culture	11 Staph. albus; 1 fungus	120 Staph. albus
3. Colectomy	1 Staph. aureus	1 Staph. citreus	32 Staph. albus and citreus	10 Staph. albus
4. Posterior gastroenterostomy	Uncountable B. subtilis; 1 Staph. albus	5 B. subtilis	1 Staph. albus	Uncountable B. subtilis; 1 Staph. albus
5. Radical mastectomy	2 Staph. albus	No culture	12 Staph. albus; 1 fungus	31 Staph. albus; 2 fungi
6. First stage thoracoplasty	No growth	No growth	No growth	1 Staph. albus; 1 fungus
7. Repair of ventral hernia	32 Staph. aureus and albus	48 Staph. albus and citreus	12 Staph. albus	75 Staph. albus
8. Subtotal thyroidectomy	3 fungi	No growth	1 Staph. albus; 2 fungi	80 Staph. albus; 2 fungi
9. Exploratory laparotomy	No growth	2 Staph. albus	12 Staph. albus	82 Staph. albus
10. Radical mastectomy	No growth	No culture	1 Staph. albus	138 Staph. albus

A large number of organisms were obtained from the surface of the skin after closure of the wound. This was thought to be due to the resident flora rising to the surface and multiplying during the time of the operation.

The number and type of bacteria obtained from the surface of the skin immediately after mechanical and chemical cleansing did not vary greatly with the character or location of the operation. This is demonstrated in table 2. Thorough cleansing removed most of the transient flora, and the number of bacteria carried into the wound with the knife was small, regardless of the location of the operation. The number of bacteria removed from the wound before closure was greater in the operations for inguinal hernia than in those listed in the second table. A greater number were also removed from the surface of the skin at the end of the operation. This is thought to be due to the presence of numerous hair follicles in this region, resulting in a larger resident flora.

COMMENT

During most clean operations, bacteria from the skin gain entrance to the wound. The majority of these belong to the resident flora and generally do not cause serious infection. The most common organism removed from the surface of the skin and the operative wound after thorough mechanical and chemical cleansing is Staph. albus. This organism does not cause serious infection unless present in very large numbers. Staph. albus occasionally causes stitch abscesses, especially when the stitches are tied too tightly or left in place a long time. Examination of the wounds in the cases in which cultures were taken revealed only one stitch abscess. In some instances, Staph. aureus was recovered from the wound but the number was small. In 1 case, a large number of E. coli were recovered from the wound owing to contamination with bile during cholecystectomy. Culture of the contents of the gallbladder grew these organisms. There was considerable discharge from the stab wound made for drainage, but no gross infection of the wound occurred.

Although the presence of a relatively large number of resident bacteria may not cause gross infection with suppuration in a clean operative wound, such bacteria should not be disregarded. They may cause prolonged elevation of the postoperative temperature. Excessive pain, redness and induration of the wound also may result from low grade infection caused by these organisms. In the presence of avitaminosis and other nutritional, systemic or local conditions, they may be factors in delaying healing of the wound, thereby predisposing to disruption of the wound and postoperative hernia. They may cause stitch abscesses or may lead to excessive scarring. Frequently they cause low grade chronic infection around subcutaneous suture material, leading to draining sinuses, and in many instances the sutures must be removed before proper healing takes place.

During operation, the skin should be considered contaminated at all times, regardless of the preoperative preparation. The skin should not be touched with gloved hands or instruments that are to be used during the remainder of the procedure. After the incision in the skin has been made, the knife used should be discarded and not used again except for prolonging the incision. The skin should then be covered with sterile towels, which are fastened in place with clips, care being taken not to leave the skin edges uncovered. These towels should be left in place until the wound is closed to the subcutaneous fascia. At this time, the surface of the skin should be considered much more contaminated than at the time the original incision in the skin was made. The towels should then be removed, the surface of the skin cleaned with the antiseptic solution and clean sterile towels placed over the area before the sutures are inserted in the skin. This reduces the bacterial contamination of the subcutaneous tissues and thereby results in fewer bacteria about the subcutaneous and the cutaneous sutures. Stitch abscesses are best avoided by the additional precautions of early removal of the suture and avoidance of tension.

SUMMARY

The number and types of bacteria of the skin gaining entrance to clean operative wounds have been studied by means of cultures. The most common organism gaining entrance to the wound is Staph. albus. It is thought that this organism is not usually responsible for serious infection in wounds but may cause other reactions in wounds. In some instances bacteria that are more pathogenic gain entrance to clean wounds but not in sufficient numbers to cause serious infection if proper technic is used.

The high probability of the entrance of bacteria into every operative wound should be a constant challenge to reduce such contamination. Common sense dictates that the wound be left in the best possible condition for healing, and the presence of these bacteria makes it imperative that the tissues be left in the best possible condition for combating this bacterial growth.

PENICILLIN IN THE TREATMENT OF CHRONIC OSTEOMYELITIS

A PRELIMINARY REPORT

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The history of the treatment of chronic osteomyelitis is replete with many rebuffs to the suffering victims, despite the application of many new procedures and drugs and serums which have been developed in recent decades. Notwithstanding the fact that these new approaches have produced spectacular results in the treatment of other types of infections, they have been found wanting in the treatment of chronic osteomyelitis. These failures are due to the inherent nature of the chronic osteomyelitic lesion. Many hopes, raised high with the advent of every new therapeutic agent, have met with disappointment due to the lack of appreciation of the differences existing between the chronic osteomyelitic lesion and other lesions and the specialized problems involved in the cure of the disease under consideration

Rational therapy can be administered only when the pathologic character of the involvement is appreciated. Briefly, the chronic osteomyelitic lesion presents a diseased bone which has undergone changes during the processes of destruction and of ineffectual attempts at healing. The destructive processes are manifested by the presence of cavities of varying size containing indolent or infected granulation tissue or pus, which may or may not yield micro-organisms on culture. These cavities may possibly contain one or more sequestrums or fibrous tissue scars and may or may not communicate with the surface of the bone or limb by sinus tracts lined with dense scarred fibrous tissue. The reparative processes are manifested by subperiosteal and endosteal new bone formation, with resultant obliteration of some of the haversian canals and the medullary canal and thickening of the cortex of the bone. These processes result in the deformation of the over-all shape and contour of the bone and the conversion of the diseased area into an ivory-like mass of dense bone. The sequestrums and cavities and their contents are devoid of a vascular supply, while the sclerotic bone presents a greatly diminished vascular tree. The periosteal covering of such a bone is thickened, fibrous and scarred as a result of the long-standing inflammatory process, and its vascularity is therefore greatly diminished. The soft tissue cloak of such a bone is usually in part a densely cicatrized, poorly nourished mantle resulting from long-standing stasis of blood and lymph incidental to the chronic inflammatory process and frequently to the scars of previous operative procedures and of intermittent healing of sinus tracts.

It is therefore evident that one of the most important characteristics of the lesion is its poor blood supply. The contents of the bone cavities, such as pus and sequestrums, are completely avascular and therefore beyond the reach of any therapeutic agent carried by the blood stream, be it chemical or biologic. Nevertheless, there were persons who believed in vain in days gone by that the intravenous administration of merbromin or gentian violet, and more recently that the intramuscular administration of staphylococcus toxoid or the local administration of bacteriophage, would be sufficient to overcome the chronic osteomyelitic lesion. By the same token, there are now those who would depend on the "miracle" drug sulfanilamide and its derivatives or the "wonder" drug penicillin. The administration of these agents as the sole mode of therapy for chronic osteomyelitis has met with failure, even though there is at times clinical relief of symptoms. This relief is, however, temporary. Dependence on this relief is harmful, for the local osteomyelitic lesion, as demonstrated by the roentgenographic changes over a period of time and the subsequent observations at operation, progresses to become more extensive and even inoperable, while the micro-organisms may perhance become more resistant to the chemotherapeutic agent.

It is characteristic of chronic osteomyelitis to produce exacerbations of clinical symptoms of pain, tenderness, low grade fever, malaise and

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Hospital for Joint Diseases. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

loss of weight without necessarily breaking down to discharge pus. The subsidence of the symptoms, which at times occurs spontaneously or as the result of medications of many varieties or even of mere immobilization, does not mean that the process at the site of the lesion has subsided. On the contrary, serial roentgenographic studies have shown that the lesion progresses, as is indicated by increasing sclerosis and bone production in the area surrounding the focus and the enlargement of the areas of rarefaction. In consequence of this knowledge, one can hardly attribute special merit to penicillin or any other drug unless its effects have been followed both clinically and roentgenographically for many years.

It has been shown that penicillin is effective against susceptible organisms only when they are actively growing,[1] and also that with an adequate concentration of penicillin the rate of killing proceeds in inverse ratio to the number of organisms originally present.[1a] Furthermore, in vitro experiments have shown that while the majority of organisms in a very heavy original inoculum are killed by penicillin a few may remain viable.[2] Rammelkamp and Keefer have suggested that these organisms survive either because they are not dividing or because they have become resistant to penicillin.[2a] If a similar situation exists in the body, the difficulty of sterilizing abscess cavities becomes apparent.[2b] This is especially true of osteomyelitic lesions, in which the surviving organisms may later reactivate the infection.[3a]

From the aforementioned facts it appears to be of fundamental importance that, in order to provide opportunity for penicillin to act, the administration of the drug must be accompanied with surgical removal of infected material. The necessity for adequate surgical procedures in conjunction with penicillin therapy of lesions of bone has been repeatedly stressed in the literature.[3]

The treatment of chronic osteomyelitis involves two problems: first, control of the infection and, second, removal of infected necrotic tissue and preparation of the area for subsequent healing. The former can be accomplished ideally by complete sterilization of the focus, while the latter can be accomplished only by adequate surgical treatment. Both problems are closely related and are in fact parts of the same large problem of therapy. Unless accompanied with effective control of the infection, surgical intervention cannot be expected to yield its best results, nor can the use of even large amounts of an antibacterial agent be of greatest value unless necrotic tissue is removed from the infected area. The use of penicillin appears to offer great promise in control of the infection, but certain facts must be kept in mind.

Were it possible to sterilize a chronic osteomyelitic focus by the mere administration of any drug, one would still be left with a focus which possessed great potentialities for relighting of the disease due to the presence of devitalized and poorly vascularized tissues. Furthermore, the presence of infection is not the only prerequisite for the occurrence of symptoms, as is shown by the occasional finding of a sterile Brodie abscess or a sterile sclerosing type of osteomyelitis. It must therefore be evident that the treatment of chronic osteomyelitis involves, in addition to the control of the infection, the eradication of the focus surgically. That this premise is true is borne out by past experiences with other medications and present experience with penicillin. Several of the patients treated by the technic to be described gave histories of extensive use of penicillin with but fleeting, if any, alleviation of the condition. The experiences of one of our colleagues at the Hospital for Joint Diseases clearly demonstrated the ineffectiveness of penicillin when used as the exclusive therapeutic agent without eradication of the focus. Our own experiences have clearly indicated that in those instances in which the eradication of the focus is

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2. (*a*) Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphlyococcus Aureus, J. Clin. Investigation **22**:649-657 (Sept.) 1943. (*b*) Rantz, L. A., and Kirby, W. M. M.: The Action of Penicillin on the Staphylococcus in Vitro, J. Immunol. **48**:335-343 (June) 1944.

3. (*a*) Bloomfield, A. L.; Rantz, L. A., and Kirby, W. M. M.: The Clinical Use of Penicillin, J. A. M. A. **124**:627-633 (March 4) 1944. (*b*) Dawson, M. H., and Hobby, G. L.: The Clinical Use of Penicillin: Observations in 100 Cases, ibid. **124**:611-622 (March 4) 1944. (*c*) Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, S. B., Jr.: Penicillin in the Treatment of Infections: A Report of 500 Cases, ibid. **122**:1217-1224 (Aug. 28) 1943. (*d*) Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, ibid. **123**:1007-1018 (Dec. 18) 1943. (*e*) Barr, J. S.: The Use of Penicillin in the Navy, J. Bone & Joint Surg. **26**:380-386 (April) 1944. (*f*) Herrell, W. E.: The Clinical Use of Penicillin: An Antibacteral Agent of Biologic Origin, J. A. M. A. **124**:622-627 (March 4) 1944. (*g*) Bloomfield, A. L.; Kirby, W. M. M., and Armstrong, C. D.: A Study of "Penicillin Failures," ibid. **126**:685-691 (Nov. 11) 1944. (*h*) Anderson, D. G.; Howard, L. G., and Rammelkamp, C. H.: Penicillin in the Treatment of Chronic Osteomyelitis: A Report of Forty Cases, Arch. Surg. **49**: 245-257 (Oct.) 1944. (*i*) Meleney, F. L.: The Difficulty of Evaluating Drug Treatment in Surgical Infection, J. A. M. A. **124**:1021-1026 (April 8) 1944.

not feasible surgically or has not been complete for one reason or another recurrence has been the rule. Furthermore, in patients with multiple lesions the surgical attack on one of the lesions in association with the use of penicillin will result in the healing of the lesion subjected to operation, while the other lesions remain uninfluenced until such time as they are in turn subjected to operative therapy in conjunction with the administration of the drug.

The necessity for the surgical eradication of the osteomyelitic lesion creates of itself the difficult problem of healing the resultant rigid-walled cavity. The only exceptions are those instances in which amputations are performed. Healing can be accomplished by one of two methods. The usual method resorted to in recent times depends on the filling of the rigid-walled cavity with granulation tissue from the depth and periphery of the wound to its surface and the subsequent epithelization of the débrided area. The success of this method depends largely on the speed with which these granulations fill the wound. Unfortunately, the growth of granulation tissue proceeds satisfactorily to a certain point, subsequent to which growth becomes unequal in various parts of the wound and unduly prolonged. Healing finally comes to a standstill in many instances, resulting in the formation of sinuses and failure of closure of the wound. This is due to the gradual conversion of the aging granulation tissue at the periphery of the wound into fibrous tissue, resulting in the shutting off of the blood supply, as is characteristic of the formation of scar tissue. It therefore becomes evident that this method of healing of the saucerized area depends chiefly on the rapidity with which the granulation tissue proliferates to fill the cavity, for any undue delay results in the shutting off of the blood supply by the normal process of cicatrization.

The second method of healing of the saucerized area depends on various plastic procedures to obliterate or fill the rigid-walled cavity in association with primary or delayed closure of the wound. The use of foreign substances was formerly resorted to in an effort to obliterate the dead space. These procedures have usually failed because the antibacterial agents hitherto available were unable to control the element of infection of the hematoma, which perforce is present to a varying degree.

EXPERIMENTAL STUDIES

It is with these thoughts in mind—namely, the past history of the trials and the tribulations of the therapy of chronic osteomyelitis,[4] the pathologic status of the lesions and the problems encountered in the healing of this stubborn disease—that we have undertaken the project to study the usefulness of penicillin against this dread disease under a contract between the Office of Scientific Research and Development and the Hospital for Joint Diseases, on the recommendation of the Committee on Medical Research.

Procedures.—Each case was subjected to a painstaking review of the patient's history, physical observations and serial roentgenograms (when available), in order to evaluate the previous course of the disease. Bacteriologic examination included repeated cultures of the lesions and determinations of the susceptibility of the organisms to penicillin. Studies of the effect of the development of resistance to penicillin on the pathogenicity and physiologic processes of the organisms will be the subject of a separate report. Repeated determinations were made of the concentration of penicillin in the blood and urine of each patient by the method described by Rammelkamp.[5] In several instances the bone removed at operation was tested for the presence of penicillin. As a consequence of the observations cited in the introductory remarks, all but a few of the patients were subjected to an extensive saucerization operation.

Dosage.—With a few exceptions, all the patients received 20,000 units of penicillin intramuscularly every three hours. Infants and young children were given 10,000 units, as were also a few of the adults treated at the outset of this project. The duration of penicillin therapy depended on the clinical course of the patient. The total dose for each patient is recorded in tables 1 to 4.

In general, the size of the dose of penicillin administered was reflected in the concentration of penicillin in the patient's blood and urine. With a constant dose, the concentration of penicillin in successive samples of blood and urine from the same patient tended to be fairly constant. Raising or lowering the dose generally resulted in an increase or a reduction, respectively, of the blood level of the drug. However, variations

4. Buchman, J., and Blair, J. E.: Maggots and Their Use in the Treatment of Chronic Osteomyelitis, Surg., Gynec. & Obst. **55**:177-190 (Aug.) 1932. Buchman, J.: Rationale of the Treatment of Chronic Osteomyelitis with Special Reference to Maggot Therapy, Ann. Surg. **99**:251-259 (Feb.) 1934. Blair, J. E., and Hallman, F. A.: Staphylococcal Antihemolysin-Titers Following Staphylococcal Toxoid in Chronic Osteomyelitis, Proc. Soc. Exper. Biol. & Med. **34**:637-642 (June) 1936. Buchman, J.: The Use of Staphylococcus Toxoid in the Treatment of Chronic Osteomyelitis, J. A. M. A. **108**: 1151-1156 (April 3) 1937; The Rationale and Results of Maggot Therapy in Chronic Osteomyelitis, New York State J. Med. **39**:1540-1553 (Aug. 15) 1939; The Treatment of Chronic Osteomyelitis, S. Clin. North America **122**:581-595 (April) 1942; Osteomyelitis, in Litchfield, H. R., and Dembo, L. H.: Therapeutics of Infancy and Childhood, Philadelphia, F. A. Davis Company, 1942, vol. 4, chap. 87, pp. 3732-3768.

5. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**:95-97 (Oct.) 1942.

among individuals occurred, for the same dose in different patients did not necessarily result in similar penicillin levels. Comparable observations have been reported by Cooke and Goldring.[6] Confirming numerous reports in the literature, we found that the highest concentrations of penicillin in the blood were obtained during the first thirty minutes to one hour after intramuscular injection. The titers dropped off rapidly after the first hour or two. In 85 per cent of the cases studied, the penicillin blood levels were greater than, or equal to, the concentration of penicillin which killed the infecting staphylococcus in vitro.

On the whole, relatively low blood levels of penicillin were accompanied with a high rate of excretion of penicillin in the urine. Conversely, when the blood levels were appreciably higher, proportionately less penicillin per cubic centimeter was found in the urine. In 1 case of renal amyloidosis, excretion of penicillin in the urine never exceeded 5 units per cubic centimeter, while the blood levels consistently remained at 0.3 to 0.6 unit per cubic centimeter. The effect of impaired renal function on penicillin levels in the blood has recently been noted by Cooke and Goldring.[6]

Classification of Patients.—The patients in this series may be placed in two main categories: (*a*) those receiving penicillin but not subjected to surgical therapy (group 1) and (*b*) those receiving penicillin plus surgical intervention. In view of the modifications of surgical treatment which were adopted as a result of our observations, the second category is further subdivided into three groups, namely, group 2, the patients with lesions which were left open and were allowed to heal by granulating from the bottom and periphery of the wound, with resultant healing by secondary intention; group 3, those with lesions which were subjected to delayed closure of the wound and were allowed to heal by delayed primary closure, and group 4, those with lesions which were closed without drainage and were allowed to heal by primary intention. The results obtained in the four groups are given in the following section.

RESULTS

Group 1.—In the first group are included those patients who could not be subjected to surgical treatment because either the location or the extent of the lesion made it technically impossible to remove the focus. In the case of patients with multiple lesions, the surgical therapy of one of the lesions in association with the use of penicillin gave the opportunity to observe the effect of penicillin on the remaining lesions, which for the moment were being treated conservatively. The patients with conservatively treated lesions are therefore listed in group 1, even though they were later included in another category, when they were subjected to surgical intervention.

The material for culture was necessarily obtained from draining sinuses of the patients in this group. A coagulase-positive Staphylococcus aureus was isolated in every instance. As might be expected, one or more than one secondary organism was frequently found in cultures together with the staphylococci. Various secondary organisms were encountered: Bacillus pyocyaneus, gram-negative bacilli of the colon group, Bacillus subtilis, micrococci and diphtheroid bacilli. They tended to persist together with the staphylococci throughout the period of observation. The staphylococci isolated in successive cultures from a patient usually retained their original sensitivity to penicillin; in 1 instance an increased resistance from 0.06 to 20 units developed over a period of three and one-half weeks. In 1 instance in which penicillin therapy resulted in complete failure (amputation was ultimately necessary) the coagulase-positive Staph. aureus responsible for the infection grew readily in 20 units of penicillin on original isolation.

Table 1 shows all of the pertinent data concerning lesions treated by the administration of penicillin without resort to surgical intervention. Of 17 lesions, only 3 were favorably influenced. One of these (26-38) was an inflammatory mass which had not as yet suppurated, and another (50-71) was a superficial carbuncle of the leg which would possibly have done as well without the penicillin. The third (33-50) was an injury to a recently healed focus treated by saucerization, primary closure and preoperative and postoperative administration of penicillin, with no evidence of suppuration or sequestrum formation. Aside from the last-cited instance, there was not a single instance of chronic osteomyelitis which was influenced beyond momentary healing and improvement in the general well-being. One lesion (52-76), a small soft tissue abscess, was aspirated several times, and 20,000 units of penicillin was instilled on each occasion. In addition, the patient was given 20,000 units intramuscularly every three hours until subsidence of accumulations within the abscess, sterilization of aspirated material from the abscess and subsidence of all symptoms occurred in about seven days. Notwithstanding all this, the lesion promptly recurred, necessitating surgical drainage. It is therefore evident, even from this small group of lesions, that little can be expected from the use of penicillin to the exclusion of surgical intervention.

Group 2.—Our experiences with but a few cases soon led us to the realization that from the point of view of the time element and the nature of healing of the wound little was to be gained by

6. Cooke, J. V., and Goldring, D.: The Concentration of Penicillin in Various Body Fluids During Penicillin Therpay, J. A. M. A. **127**:80-87 (Jan. 13) 1945.

resort to the method of healing by granulation tissue formations from the depth and periphery of the wound. The failure of penicillin to shorten the healing period in these cases was not at all unexpected. It was observed that penicillin, even if administered over prolonged periods, locally as well as intramuscularly, did not hasten the separation of slough from the wound, nor did it hasten the growth of granulation tissue.

Furthermore, bacteriologic studies revealed that within a few days after operation secondary invaders invariably appeared and persisted till closure of the wound. The secondary invaders usually found were B. pyocyaneus, Bacillus proteus, gram-negative bacilli of the colon group, B. subtilis, micrococci and occasionally streptococci. With only one exception, the coagulase-positive staphylococci persisted till final closure.

TABLE 1.—*Lesions Treated by the Administration of Penicillin Without Resort to Surgical Intervention*

Case and Lesion No., Age, Sex	Lesions: Site	Lesions: Duration, Yr.	Lesions: Other Lesions	Penicillin: Dose, Thousand Units	Penicillin: Duration, Days	Penicillin: Local, Days	Penicillin: Total Amount, Thousand Units	Comment
1-1 20 M	Lumbar spine	7	Multiple foci; amyloidosis; blood dyscrasia	30 15 10 5	19	23	1524	Sinus of back closed on 23d day after start of treatment but recurred 33 days later; sinus in groin closed on 16th day but recurred 4 months later; other sinuses have recurred; general condition improved
3-5 28 M	Tibia	10 mo.	Spine	10	9	0	686	Lesion in tibia uninfluenced during administration of penicillin following operation on spine, which healed; same lesion later subjected to surgical treatment plus penicillin and healed; see table 2, lesion 3-6
5-8 63 M	Tibia and fibula	26	Lymphedema and ulcer, same leg	15	18	0	1870	Complete failure; limb subsequently amputated.
25-36 26 F	Hip	14	None	20	15	0	2240	Temperature and symptoms subsided at first then recurred; temperature began to rise when penicillin was discontinued; after subsequent operation plus penicillin symptoms disappeared; see table 4, lesion 25-37
26-38 57 F	Inflammatory mass in groin	2 days	Metatarsal; diabetes	10	16	0	1170	Mass was aspirated, but no pus could be obtained; suppuration had not as yet taken place; resolved completely
26-39 57 F	Metatarsal	1	Inflammatory mass in groin; diabetes	10	16	0	1170	Completely unaffected by administration of penicillin during treatment of lesion 26-38 (above), which healed; see table 4, lesion 26-40, for response to surgical treatment plus penicillin
27-42 27 M	Tibia	15	Multiple	20 10	12	0	1483	Lesion unaffected, while humerus (table 4, lesion 27-41, subjected to surgical treatment) healed
7-12 26 F	Tibia	23	Multiple	10	22	0	1810	Ulcer healed on 25th day; broke down 1 month later, while lesion of elbow (table 2, lesion 7-13) healed; see table 4, lesion 7-75, for healing subsequent to surgical treatment plus penicillin
7-11 26 F	Elbow	23	Multiple	10	10	0	750	Unaffected; tenderness and pain persisted; see table 2, lesion 7-13
50-71 26 M	Carbuncle of leg	4 wks.	Ilium and carbuncle of axilla	20 10	12	0	1450	Healed on 12th day; see table 1, lesion 50-72; table 2, lesion 50-70, and table 4, lesion 50-73
50-72 26 M	Ilium	15	Carbuncles of leg and axilla	20 10	12	0	1450	Completely uninfluenced; see table 1, lesion 50-71; table 2, lesion 50-70, and table 4, lesion 50-73
33-50 22 M	Femur	7	None	20	7	0	1000	Symptoms subsided in 7 days; there was no suppuration present; see table 4, lesion 33-49
52-76 37 M	Soft tissue abscess	1 wk.	Tibia (inactive)	20	12	2	1780	Failure; appeared to be healed on discharge but recurred in 10 days; see table 2, lesion 52-77
55-80* 24 M	Ilium	20	.....	10	7	..	470	Failure: temperature subsided in 4 days; recurred in 7 days
55-81* 24 M	Ilium	20	.....	10	14	7	1058	Completely uninfluenced; symptoms did not begin to subside until abscess was drained
61-88* 25 M	Tibia and fibula	1	.....	10 q4h	10	..	600	Failure
61-90* 25 M	Tibia and fibula	1½	.....	15 q4h	21	3	1745	Failure

* Patients treated by other members of the orthopedic staff and included through their courtesy.

The persistence of the staphylococci over these long periods was often accompanied with a definite tendency for the organism to become increasingly resistant to penicillin. For example, one strain was originally killed by 0.06 unit of penicillin; seven weeks later 1.25 units was re-

quired to kill it, and after another four weeks it grew readily in a concentration of 1,000 units per cubic centimeter. Another strain, also originally killed by 0.06 unit, developed an eighty fold resistance in a week and two weeks later grew in a concentration of 20 units per cubic centimeter.

Table 2 indicates the essential data concerning lesions treated by the preoperative and postoperative administration of penicillin in conjunction with surgical intervention, in the form of as thorough a saucerization as was feasible in the circumstances. The wounds were left open and were permitted to heal by granulations. In this group of 9 patients healing of the lesions has occurred in all instances and there has been no recurrence during the period of observation, which is admittedly of short duration. Further analysis reveals that the healing period is prolonged, except for those patients for whom it was possible to collapse the wounds This method of therapy therefore yields little or no advantage over previous routines of therapy.

Group 3.—In view of the failure of penicillin to exert a positive influence on the time element of healing by granulations; in view of the failure of penicillin to control the primary or the secondary bacterial invaders, and in view of the development of pronounced resistance to penicillin on the part of the primary invaders and the relatively absolute resistance on the part of the secondary invaders, we abandoned this method of therapy.

We thereupon resorted to the method of healing of the saucerized focus by delayed closure. Interrupted sutures were inserted and left untied, and the wounds were packed with gauze soaked with isotonic solution of sodium chloride containing 250 units of penicillin per cubic centimeter. In the later cases, the wounds were packed with gauze impregnated with fatty acid esters of diethanolamine with petrolatum (Hydrosorb) containing 1,000 units of penicillin per gram. Dry dressings were applied, and the parts were immobilized in compression dressings of sheet wadding, flannel bandage and adhesive. Several days later, the packings were removed and the sutures were tied. The results obtained were gratifying in that closure of wounds occurred in a

TABLE 2.—*Lesions Treated by the Administration of Penicillin and Saucerization; Wounds Allowed to Heal by Granulation*

	Lesions			Penicillin				Cultures					
Case and Lesion No., Age, Sex	Site	Duration, Yr.	Other Lesions	Dose, Thousand Units	Duration, Days	Local, Days	Total Amount, Thousand Units	Preoperative	At Operation	Postoperative	Increased Resistance	Date of Operation	Comment
3-6 28 M	Tibia	10 mo.	.....	10	16	57	1250	Sa Si	Sa	Sa Si	0	6/ 6/44	Healed in 63 days; rate of healing not materially influenced; see table 1, lesion 3-5 and table 3, lesion 3-4; healed 9 months postoperatively
4-7 21 M	Metatarsal	8½	Hip (inactive)	10	15	61	1063	Sa	Sa	Sa Si	+	5/15/44	Healed in 61 days; rate of healing not shortened; healed 9 months postoperatively
6-10 19 M	Femur	1½	None	10	17	53	1364	Sa Si	..	Sa Si	0	5/27/44	Healed in 81 days; rate of healing not materially influenced; healed 9 months postoperatively
8-14 21 M	Tibia	7½	None	10 5	74	75	3853	Sa Si	Sa	.. Si	..	6/14/44	Healed in 6 months; rate of healing not influenced; healed 9 months postoperatively
9-15 60 F	Tibia	Many	None	10	14	45	1288	Sa	Sa	Sa Si	+	6/14/44	Pinch graft on 104th postoperative day; healed on 143d day; rate of healing not influenced; healed 9 months postoperatively
23-33 39 M	Tarsus and metatarsal	23	None	20 10	12	21	1424	Sa	Sa	Sa Si	+	10/10/44	See table 3, lesion 23-32; wound allowed to collapse; healed 3 months postoperatively
7-13 36 F	Elbow	23	Tibia (multiple)	10	12	32	1060	..	Sa	.. Si	..	6/20/44	Wound healed in 2 months; healed 9 months postoperatively
50-70 20 M	Carbuncle of axilla	4 wk.	Ilium; carbuncle of leg	20 10	12	12	1450	Sa	..	.. Si	..	12/12/44	Healed in 17 days; see table 1, lesions 50-71 and 50-72 and table 4, lesion 50-73
52-77 37 M	Soft tissue abscess	? wk.	Tibia (inactive)	20	10	5	1340	..	Sa	Sa Si	+	3/20/45	Healed in 3 weeks; healed 1 month postoperatively; see table 1, lesion 52-76

Sa — Staphylococcus aureus, coagulase positive.
Si — Secondary invaders.
\+ — Staphylococci developed increased resistance to penicillin.
0 — Staphylococci did not develop increased resistance to penicillin.

considerable shorter period than when the preceding technic was used.

In this group secondary invaders were encountered in about 80 per cent of the lesions. It is noteworthy that B. pyocyaneus and B. proteus were only occasionally found, even though other secondary invaders occurred together with staphylococci in the majority of lesions. B. pyocyaneus and B. proteus were found in only 4 of 15 wounds, and in only 2 of these did they per-

TABLE 3.—*Lesions Treated by the Administration of Penicillin and Saucerization; Wounds Subjected to Delayed Closure*

	Lesions			Penicillin				Cultures					
Case and Lesion No., Age, Sex	Site	Duration, Yr.	Other Lesions	Dose, Thousand Units	Duration, Days	Local, Days	Total Amount, Thousand Units	Preoperative	At Operation	Postoperative	Increased Resistance	Date of Operation	Comment
3-4 28 M	Spine	10 mo.	Tibia	10	9	9	686	Sa Si	Sa Si	Sa Si	+	5/ 5/44	Large saucerized area healed in 31 days; see table 1, lesion 3-5 and table 2, lesion 3-6; healed at 10 months
12-19 39 M	Radius and elbow joint	7 mo.	Tuberculosis of same elbow	20	22	15	3361	Sa	Sa	Sa Si	0	7/18/44	Diagnosis of tuberculosis made on microscopic section; operative wound healed in 4 weeks; preoperative sinus left undisturbed and continued to discharge; see table 4, lesion 12-20
13-21 36 M	Hip	24	Ankylosed hip with intrapelvic soft tissue sinus into rectum	20	10	32	1306	..	Sa	Sa Si	+	9/ 5/44	Failure; sinuses persist; surgical eradication of lesion impossible
14-22 18 F	Tuberculosis of scapula with secondary staphylococcic infection	3	None	20	16	20	2471	Sa	.. Si	.. Si	..	8/15/44	Sinus outside of operative field persisted; operative wound healed per primam
15-24 16 F	Soft tissue sinus, thigh femur	2	None	20	9	28	1196	Sa Si	.. Si	.. Si	..	8/ 8/44	Wound contaminated with B. coli; healed in 43 days; healed at 5 months
16-25 10 F	Ilium	2½	None	20	15	13	1901	Sa	Sa	Sa	0	8/15/44	Sutures tied on third day; wound healed on 14th day postoperatively
17-26 22 M	Humerus	11 mo.	Tibia; carbuncle on back	20	19	22	3440	Sa	.. St	.. St	..	8/15/44	Wound and sinus healed in 16 days; carbuncles developed on back on 36th day postoperatively; humerus healed at 6 months
18-27 29 M	Tibia	25	None	20 10	16	16	1795	..	Sa	.. Si	..	8/22/44	Failure because of slough of skin; pinch graft 7 weeks postoperatively; healed 5 weeks later; penicillin ineffective; healed at 6 months
19-28 54 F	Hip	50	None	20 10	24	29	3121	Sa	Sa	.. Si	..	8/15/44	Sinuses were not excised or closed at operation; sinuses persist 9 months postoperatively
21-30 49 M	Spine, with multiple sinuses	14	Both tibias (inactive)	20	12	25	1581	..	.. St	Si	..	8/28/44	Transversectomy performed; complete eradication of focus and extensive sinus tract impossible; all wounds healed in 4 weeks; sinuses recurred 2 months after operation
22-31 22 M	Tibia	11	None	20 10	15	10	1646	Sa	.. St	.. Si	..	8/29/44	Healed in 5 weeks; part of skin sloughed; this healed in 8 weeks; healed at 7 months
23-32 39 M	Tarsus and metatarsal	23	None	20	10	17	1273	Sa	Sa	Sa	0	9/ 5/44	Wound broke down; believed to be because of inadequate surgical treatment; see table 2, lesion 23-33
24-34 12 F	Femur	1	Metacarpal	20	12	16	1530	Sa	.. St	Sa Si	0	9/ 5/44	Sinus outside operative field not closed at operation; discharge persisted; see table 4, lesion 24-35
28-44* 50 M	Spine	9 mo.	None	20	13	15	2013	Sa	Sa	Sa Si	..	9/29/44	Sinus persisted at 9 months
48-67 14 F	Tuberculosis of hip with secondary staphylococcic infection	4	None	20 10	16	26	2176	Sa	Sa	.. Si	..	8/22/44	Healed per primam, save at one point which was subsequently found to harbor a foreign body; see table 4, lesion 48-68

* Patient treated by another member of the orthopedic staff and included through his courtesy.
Sa — Staphylococcus aureus, coagulase positive.
Si — Secondary invaders.
St — Sterile.
\+ — Staphylococci developed increased resistance to penicillin.
0 — Staphylococci did not develop increased resistance to penicillin.

sist for more than a few days. The usual secondary invaders were chiefly gram-negative bacilli of the colon group, B. subtilis and occasionally diphtheroid bacilli or micrococci. It seems that this method of closure tends somewhat to reduce the incidence of "nuisance" organisms. In 2 instances Staph. aureus was obtained in pure culture throughout the period of observation, of one to four weeks.

The development of resistance to penicillin by staphylococci in successive cultures from these wounds occurred much less frequently than in the first group. Only 2 instances of increased resistance occurred in the fifteen wounds. In the remainder the original sensitivity persisted throughout. In 1 case the resistance increased from 0.156 unit to 5 units in eleven days and in the second from 0.078 unit to 125 units in one month. In no instance in this or in the other groups was any correlation noted between the development of resistance to penicillin and the clinical course of the disease. It must be assumed that the staphylococci isolated in successive cultures in any given wound were descendants of the organism originally isolated. This seems to be borne out by the consistent sensitivities of repeated cultures when no resistance developed and by the progressively increasing titers when increased resistance did occur.

Table 3 shows the pertinent data concerning lesions treated by preoperative and postoperative administration of penicillin in conjunction with surgical intervention in the form of thorough saucerization and delayed closure of the resultant wounds. Of the 15 lesions treated by this technic, 4 (3-4, 16-25, 17-26 and 22-31) healed with spectacular rapidity, and there has been no recurrence to date. The other 11 failed to heal for various reasons: i. e., 5 (3-21, 19-28, 21-30, 23-32 and 28-44) owing to inadequate operative procedures; 3 (12-19, 14-22 and 24-34), notwithstanding the fact that the operative incisions healed satisfactorily, because sinuses outside the operative field were left untreated and were therefore instrumental in reinfecting the treated areas; 1 (48-67) because a piece of packing had been left in the wound when the delayed closure was performed; 1 (18-27) because the overlying skin sloughed, and 1 (15-24) was unduly delayed in healing because it became secondarily infected with Bacillus coli.

The data for this group clearly pointed the way to better results in that they indubitably demonstrated the necessity for the prevention of reinfection of the operated area. It became evident that the surgical attack must be most thorough and must include the sinus tracts beyond the operative field.

Group 4.—In view of the improved clinical results and bacteriologic picture obtained by delayed closure, we were emboldened to resort to primary suture of the saucerized wounds, keeping in mind various modifications in the operative technic intended to lessen the size of the resultant rigid-walled cavity. In the earlier cases merely the skin was sutured, while in the later cases the wounds were firmly closed in three layers: interrupted chronic sutures for the periosteum and muscle layers, continuous chromic gut sutures for the subcutaneous tissues and continuous silk sutures for the skin. All such wounds are now flooded with isotonic saline solution containing 250 units of penicillin per cubic centimeter. Wet dressings containing penicillin are applied, and the limbs are immobilized in compression dressings of sheet wadding, flannel bandage and adhesive. As our experience with this method increased, we found it necessary to excise or at least curet thoroughly all accompanying sinuses. The resulting wounds are also firmly sutured in order to prevent drainage from the hematoma which occurs at the operative site. Occasionally, notwithstanding the firm closure of the wound and the compression dressing, a serosanguineous or a serous discharge develops during the course of the healing of the wound. Studious neglect and absolute avoidance of probing of these sinuses has to date resulted in the healing of practically all of these wounds. All of the discharges proved to be sterile. In the presence of such a discharge the administration of penicillin was usually prolonged.

Primary closure of wounds greatly reduced the opportunities for the access of secondary invaders. Consequently, their occurrence was rare, and their presence was usually transient. In only five of the twenty-seven wounds in this group of patients were secondary bacteria consistently found. Three of these wounds had been subject to operative procedures during the previous two to five months; they had been permitted to heal by secondary closure and had had persistent secondary infection at that time. In a fourth case organisms of the colon group appeared three days postoperatively and persisted for three weeks; in the fifth, organisms of the colon group appeared one month after operation and persisted for one week. When secondary invaders occurred in a few other wounds, their presence was only transient.

Because of the success of the method of primary closure, few repeated cultures could be obtained and the periods of bacteriologic observation were relatively short. In only 3 instances were long series of successive cultures possible. Coagulase-positive Staph. aureus occurred in cultures from

all 3 wounds for periods of four to five weeks. In only 1 patient in this group did the staphylococci exhibit any development of resistance to penicillin.

Table 4 presents the pertinent data concerning the lesions subjected to preoperative and postoperative administration of penicillin, through saucerization of the foci and primary closure of the resultant wounds. Of 27 patients in this group all but 1 had lesions heal either at the time of removal of the skin sutures or soon thereafter. The lesion (50-73) which did not heal could not be subjected to adequate surgical treatment because of a very extensive, avascular soft tissue scar. This patient presented, in addition, a far advanced amyloidosis of the kidney, as was indicated by the finding of 73 mg. of nonprotein nitrogen per hundred cubic centimeters of blood serum and 100 per cent retention of congo red. The presence of hematomas was the chief complicating factor which caused delay in the healing of some of the wounds. In 1 instance (53-78) the wound broke down and drained persistently, leading to a failure of the procedure. Necrosis of the overlying skin due to embarrassed circulation was another deterrent to prompt healing in some lesions of the tibia. Notwithstanding these difficulties, healing of the wounds was consistently better and much more prompt than that obtained by any other method known to us.

To date there have been but 2 (24-35 and 27-41) recurrences among the twenty-five lesions healed as a result of the therapy instituted. Inadequate removal of the foci concerned is in all probability at the bottom of these failures.

A word should be added in explanation of the inclusion in the last two groups of several patients with tuberculous lesions of bones and joints (table 3, 12-19, 14-22 and 48-67 and table 4, 12-20, 48-68 and 51-74). All of these presented sinuses from which coagulase-positive Staph. aureus was isolated. It was our belief that if the secondary infection could be controlled surgical treatment of these lesions was both feasible and safe. The results in the few cases recorded seem to substantiate this concept. Additional experience with similar lesions should be accumulated before a definite conclusion can be warranted.

Any one who is familiar with the difficulties attendant on the evaluation of results in chronic osteomyelitis would hesitate to regard the results reported as final. We do not pretend to present them as end results. All we dare state is that the immediate results obtained from the primary closure of adequately saucerized osteomyelitic wounds in association with preoperative and postoperative administration of penicillin have been most gratifying. The follow-up period of these cases at the time of writing is admittedly short, and the eventual effectiveness of this mode of therapy can be evaluated only in the years to come.

The administration of penicillin was practically always started on the day before operation. The usual dose was 20,000 units every three hours. Cultures from draining sinuses prior to administration of penicillin and operation always yielded coagulase-positive Staph. aureus. In about one fourth of the cases the cultures made from the wound at operation were sterile. The possibility of carrying across in the inoculum an inhibitory amount of penicillin was ruled out by the use of clarase (digestive ferment of malt highly concentrated) in the culture medium or by adequate dilution in broth. Occasionally no gram-positive cocci were ever obtained in subsequent cultures, although the usual secondary organisms were occasionally present. In some instances, a few days subsequent to operation staphylococci were again isolated. These organisms were as sensitive to penicillin as the strains originally isolated. In such instance (18-27) a culture from the operative wound was sterile, but Staph. aureus was cultured from a sequestrum removed from the area.

The occurrence of sterile cultures at operation would seem to indicate that the preoperative use of penicillin permits a fairly good temporary control of the infection. The relatively few staphylococci remaining at the time of operation are inhibited for a short time, but in the majority of instances, even with continued penicillin therapy, the survivors ultimately develop sufficiently to be demonstrable in the subsequent cultures. Whether or not temporary sterilization will occur in a given instance probably depends in part on the number of staphylococci in the lesion before operation. It is known that the probability of survival of a few organisms is greater if the number originally present is very high.[7]

The temporary control of the infection raises the question of the amount of penicillin which can get into the bone during penicillin therapy. Bone chips removed at operation were infused in isotonic solution of sodium chloride (approximately 10 Gm. of bone in 10 cc.) for twenty-four to forty-eight hours at 10 C. The infusion was decanted, centrifuged and tested for penicillin activity by the Oxford cup plate method. Of eighteen samples of bone treated in this manner, sixteen showed no measurable amount of penicillin. In two specimens, titers of 0.015 and 0.03

7. Footnotes 1 *a* and 2.

TABLE 4.—*Lesions Treated by the Administration of Penicillin and Saucerization; Wounds Subjected to Primary Closure*

Case and Lesion No., Age, Sex	Lesions: Site	Lesions: Duration, Yr.	Lesions: Other Lesions	Penicillin: Dose, Thousand Units	Penicillin: Duration, Days	Penicillin: Local, Days	Penicillin: Total Amount, Thousand Units	Cultures: Preoperative	Cultures: At Operation	Cultures: Postoperative	Cultures: Increased Resistance	Date of Operation	Comment
10-17 13 M	Tibia	6 mo.	None	20	23	3	3313	Sa	Sa	Sa Sl	0	12/ 5/44	Penicillin discontinued on 9th day because of severe angioneurotic edema and urticaria; sinuses appeared; use of drug started again 2 weeks later; sinuses healed 5 weeks postoperatively; healed at 3 months
12-20 39 M	Elbow joint	10 mo.	None	20 10	16	3	2160	Sa Sl	Sa Sl	.. St	..	11/ 7/44	Elbow resected; sinus curetted and sutured; wound healed per primam; healed at 10 weeks; this is a tuberculous elbow with secondary staphylococcic infection
24-35 12 F	Femur	1	Metacarpal	20 10	29	6	3626	Sa Sl	.. Sl	Sa Sl	0	11/ 7/44	Healed at 11 weeks; a very large cavity remained after operation, with resultant hematoma which broke through on several occasions; remained healed for 4½ months when a sinus developed
25-37 26 F	Hip	14	None	20	10	At op.	1460	..	St	*	..	10/10/44	Intra-articular and extra-articular arthrodesis performed; surface layers of bone of head of femur and acetabulum removed; healed per primam; healed at 5 months; see table 1, lesion 25-36
26-40 57 F	Metatarsal	1	Diabetes	20	8	At op.	944	..	..	..	..	10/29/44	5th toe and distal 2/3 of metatarsal resected; healed per primam; see table 1, lesions 26-38 and 26-39; healed at 4½ months
27-41 27 M	Humerus	15	Tibia (active) and other lesions (inactive)	20 10	12	At op.	1483	Sa	Sa	*	..	9/26/44	Operative wound healed per primam; slight discharge from sinus which healed 4 weeks postoperatively; remained healed for 22 weeks, when sinus appeared; see table 1, lesion 27-42
30-46 17 M	Tibia	7	None	20	25	At op.	3460	..	Sa	Sa Sl	0	10/10/44	Operative wound healed per primam; overlying skin at lower angle devitalized owing to loss of circulation; this focus healed 7 weeks postoperatively; healed at 5 months
33-49 22 M	Femur	6½	None	20	12	At op.	1798	Sa	Sa	*	..	10/31/44	Healed per primam; healed at 15 weeks, when patient injured leg; followed by pain, tenderness and limitation of motion; see table 1, lesion 33-50
34-51 58 M	Tibia	7	None	20 10	15	At op.	1971	Sa	Sa Sl	.. St	..	11/ 7/44	Healed per primam save for area of necrotic skin due to embarrassed circulation; healed at 2 months; small ulcer of atrophic skin developed at 19 weeks after operation
37-54 23 M	Humerus	10	Multiple	20 10	16	At op.	2245	Sa	.. St	Sa Sl	0	11/24/44	Wound healed per primam; hematoma evacuated spontaneously; healed at 3 months
38-55 21 F	Tibia	14	None	20	11	At op.	1553	..	Sa	.. St	..	11/28/44	Healed per primam; hematoma evacuated spontaneously and 2 small areas of skin necrosis due to loss of circulation healed 5 weeks after operation; completely healed 13 weeks after operation
41-59 10 F	Metatarsal	5 mo.	None	20	19	At op.	2646	..	Sa	*	..	12/12/44	Third toe and metatarsal resected; healed per primam; healed at 3½ months
42-60 19 M	Tibia	7	Multiple; neck of femur (active)	20 10	17	At op.	2200	Sa	.. St	.. Sl	..	12/19/44	Healed per primam save for small slough which healed 3 weeks after operation; healed at 3 months
42-61 19 M	Neck of femur	7	Multiple	20	17	At op.	2598	..	St	*	..	1/16/45	Healed per primam; absorbable gauze used to obliterate cavity; wound somewhat irritated; surgical treatment may possibly be inadequate; healed at 2 months
43-62 36 M	Sacroiliac	1½	Lumbosacral	20	11	At op.	1600	..	Sa Sl	..	..	12/26/44	Resection of sacroiliac joint; healed per primam; healed at 6 weeks
47-66 15 F	Femur (L)	3	Humerus ankylosed; left hip and left knee	20 10	18	At op.	2180	Sa	.. St	Sa Sl	0	12/ 1/44	Healed per primam, but irritated; well healed in 2 weeks; healed at 2 months

TABLE 4.—*Lesions Treated by the Administration of Penicillin and Saucerization; Wounds Subjected to Primary Closure.—Continued*

Case and Lesion No., Age, Sex	Lesions: Site	Lesions: Duration, Yr.	Lesions: Other Lesions	Penicillin: Dose, Thousand Units	Penicillin: Duration, Days	Penicillin: Local, Days	Penicillin: Total Amount, Thousand Units	Cultures: Preoperative	Cultures: At Operation	Cultures: Postoperative	Increased Resistance	Date of Operation	Comment
48-68 14 F	Tuberculosis of hip with secondary staphylococcic infection	4	None	20 10	19	At op.	1960	..	Sl	Sl	..	10/24/44	Healed per primam; walked for first time in 5 years; healed at 4½ months
49-69 14 M	Tibia	3½	None	20	17	At op.	2600	..	.. * St	Sa	..	1/16/45	Healed per primam; small hematoma evacuated spontaneously; healed at 2½ months
7-75 36 F	Tibia	23	Multiple	20	17	At op.	2430	Sl	Sl	Sl	..	1/23/45	Wound healed per primam, save for serosanguineous discharge from hematoma; completely healed on 42d day postoperatively; this lesion was saucerized and plastic surgical procedures performed on the skin permit primary closure; absorbable gauze left in situ; healed 2 months after operation; see table 1, lesion 7-12
50-73 26 M	Ilium	15	Carbuncles of axilla and leg	20 10	19	14	2750	..	St	Sa Sl	0	1/ 2/45	Sinus persistent; soft tissue scar could not be excised completely; absorbable gauze left in situ; surgical treatment not adequate; amyloidosis; see table 2, lesion 50-70, and table 1, lesions 50-71 and 50-72
51-74 21 M	Ischium	3	Sinus to popliteal space	20 10	8	0	910	Sa	.. St	..	..	10/17/44	Tuberculosis of ischium with sequestrums and sinus leading to popliteal space; sinus secondarily infected with Staph. aureus; healed in 6 weeks; sinus persisted; operative site and sinus healed at 6 months
53-76 29 M	Femur	15	Right humerus and left forearm	20	20	1	3005	Sa	Sa	Sa Sl	0	2/27/45	Failure, possibly due to inadequate operation; poor general condition; persistent hematoma
56-82 28 M	Femur	12	None	20	17	1	2638	Sa	Sa	.. St	..	3/ 6/45	Healed per primam; healed at 6 weeks
57-83 2 M	Humerus	2	Ulna	10	18	1	1300	..	St	*	..	3/ 9/45	Healed per primam; healed at 4 weeks
57-84 2 M	Ulna	2	Humerus	10	18	1	1300	..	Sa	*	..	3/ 9/45	Healed per primam; healed at 4 weeks
62-89 6½ mo. F	Rib	4½ mo.	None	10	12	..	870	.. Sl	Sa Sl	*	..	3/27/45	Rib resected; healed per primam; postoperative roentgenogram shows some residual disease
54-79 23 M	Femur	4	Humerus	20	14	1	2280	Sa	.. St	Sa	+	3/20/45	Healed per primam; 2 hematomas and stitch abscesses; lesion of humerus lighted up on 8th day of penicillin therapy and subsided in 7 days

Sa — Staphylococcus aureus, coagulase positive.
Sl — Secondary invaders.
St — Sterile.
* — No cultures after operation because wounds were healed. + Staphylococci developed increased resistance to penicillin.
0 — Staphylococci did not develop increased resistance to penicillin.

unit per cubic centimeters of saline infusion were obtained. In both instances coagulase-positive Staph. aureus was isolated from the operative wounds, and both strains had sensitivities of 0.06 unit. The method is only roughly qualitative at best. Since the penicillin content of subcutaneous tissues and body fluids approximates that of the blood serum,[5] it appears probable that relatively little penicillin can penetrate the avascular sclerosed bone surrounding an osteomyelitic lesion. If this is so, it is obvious that parenteral administration of penicillin without surgical intervention cannot be expected to provide therapeutically adequate concentrations of penicillin at the site of bone lesions.

CONCLUSIONS

A clinical and bacteriologic study of the results of treatment of chronic osteomyelitis with penicillin with and without surgical intervention was made on 47 patients presenting a total of sixty-eight lesions. Some of the foci are listed in the accompanying tables more than once owing to the failure of one or another method of treatment. These are listed as separate lesions and are in-

cluded in the total. The follow-up period is indisputably insufficient and therefore makes some of the following conclusions tentative, while others are sufficiently clear to make them reasonably certain.

1. The treatment of chronic osteomyelitis with intramuscular injections and local applications of penicillin to the exclusion of surgical intervention is totally ineffective. Not a single osseous lesion or well developed soft tissue abscess was relieved by this approach.

2. The treatment of chronic osteomyelitis with preoperative and postoperative administration of penicillin, thorough saucerization of the focus and healing of the resultant wound by granulations is not materially influenced by the drug.

3. The treatment of chronic osteomyelitis with preoperative and postoperative administration of penicillin, thorough saucerization of the focus and delayed primary closure of the resultant wound is a considerable improvement over previous methods.

4. The treatment of chronic osteomyelitis with preoperative and postoperative intramuscular administration of penicillin, thorough saucerization of the focus and primary closure of the resultant wound has given extraordinarily good results in 23 out of 27 patients. The period of observation is admittedly insufficient, but the experiences to date are sufficient to warrant the continued use of this method so that it may be evaluated in its true perspective in the years to come.

5. Tuberculous lesions of bones and joints secondarily infected with coagulase-positive Staph. aureus have been subjected to thorough saucerization, primary closure of the resultant wounds and preoperative and postoperative intramuscular administration of penicillin. In a very limited number of cases primary healing has been obtained. In these cases, too, the period of observation is admittedly too short but is, nevertheless, sufficient to warrant the continued use of this method, so that it may be evaluated in its true perspective in the years to come.

6. It has been recognized that the presence of secondary organisms prolongs the period of healing of the saucerized areas. A distinct advantage of treatment by primary closure is the reduction of the opportunity for contamination of the wound by "nuisance" organisms, particularly B. proteus and B. pyocyaneus. Such organisms were invariably present in wounds allowed to heal by granulation; they occurred in 80 per cent of those treated by delayed closure but were a complicating factor in only five of the twenty-seven wounds treated by primary closure.

7. The staphylococci which persisted in wounds over relatively long periods tended to develop increasing resistance to penicillin, i. e., in wounds healing by granulation or by delayed closure. In only 1 of the patients treated by primary closure was development of resistance of the organisms noted. In no instance did increased resistance of the staphylococci occur in patients treated by penicillin without surgical intervention. The material for culture from such patients were necessarily obtained from draining sinuses. It is probable that such organisms were not exposed to the penicillin administered intramuscularly because of the relatively avascular nature of the thickened fibrous walls of the sinuses and the avascularity of the lesions in which they originated.

Treatment of patients in connection with this article was carried out at the Hospital for Joint Diseases. Miss Miriam Carr assisted in the bacteriologic studies.

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POST-TRAUMATIC RENAL INJURY

SUMMARY OF EXPERIMENTAL OBSERVATIONS

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Early and adequate transfusion, prevention of infection and improved supportive measures are responsible for the survival of an untold number of casualties whose injuries would formerly have been rapidly fatal. But the very survival of persons seriously injured raises new problems in traumatotherapy, among which anuria assumes increasing significance. This report summarizes clinically relevant observations made during an experimental study of post-traumatic renal injury.

The effects of trauma on renal function vary widely, according to the nature, severity and duration of the injury. Hemorrhage which does not cause prolonged hypotension usually results in temporary anuria, which is corrected by transfusion and which has no more significant sequel than the transitory appearance in the urine of casts, protein and red blood cells. Prolonged shock from hemorrhage or skeletal trauma may be followed by oliguria or anuria which does not respond to transfusion and culminates in uremia, although no specific renal lesion can be recognized. Shock associated with damage to skeletal muscle may be followed by renal failure, for which pigment casts within the renal tubules suggest participation of muscle pigment, myoglobin, as a cause.

The latter condition was recognized and named "crush syndrome" in a study of cases occurring during the London blitz.[1] Prior reports of similar cases in the German army of 1914 to 1918[2] and in accidents in civil life[3] were largely overlooked. This seeming neglect probably resulted from the fact that until recently patients whose injuries predisposed to this complication of trauma died from shock or sepsis before renal failure became apparent.

Crush syndrome is initiated by direct compression or arterial occlusion of skeletal muscle, usually of the leg. Release from pressure or restoration of blood flow is generally followed by shock, which responds to transfusion. The injured limb swells and becomes hard and paralyzed. Urine formed during the first hours is reddened with myoglobin, present in oxy and meta forms in amounts which may exceed 3 Gm.[4] Other substances normally contained in the muscle cell, notably creatine, phosphate and potassium, also appear in the urine in large amounts, apparently because of their diffusion from the ruptured muscle cells into the blood. Creatinuria and hyperpotassuria may be partly due to the increased protein catabolism which follows injury,[5] but the coincidence of myoglobinuria is an indication of actual muscular disruption.[6]

During subsequent days, urinary volume and specific gravity decrease; vomiting and delirium with azotemia, hyperpotassemia and moderate arterial hypertension supervene. Death may occur suddenly about the fifth day, with some evidences of potassium intoxication, or in patients who are to recover urinary volume may begin to increase at this time. Complete recovery of renal function may require several months.

The renal lesions consist principally in moderate degenerative changes (cloudy swelling and droplet degeneration) of proximal convoluted tubules. In the wide ascending loop of Henle and the distal tubule are deposits of hyaline and pigment casts, sometimes in crystalline form.

From the Cleveland Clinic Foundation.

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1. Bywaters, E. G. L., and Beall, D.: Crush Injuries with Impairment of Renal Function, Brit. M. J. **1**:427-432 (March 22) 1941. Mayon-White, R., and Solandt, O. M.: Case of Limb Compression Ending Fatally in Uraemia, ibid. **1**:434-435 (March 22) 1941.

2. Minami, J.: Ueber Nierenveränderungen nach Vershüttung, Virchows Arch. f. path. Anat. **245**:246-247, 1923.

3. Husfeldt, E., and Bjering, T.: Renal Disturbances in Traumatic Shock, Hospitalstid. **78**:781-792 (July 23) 1935.

4. Bywaters, E. G. L.; Delory, G. E.; Rimington, C., and Smiles, J.: Myohaemoglobin in the Urine of Air Raid Casualties with Crushing Injury, Biochem. J. **35**:1164-1168 (Nov.) 1941.

5. Cuthbertson, D. P.: Post-Shock Metabolic Response, Lancet **1**:433-436 (April 11) 1942.

6. Bywaters, E. G. L.: Crushing Injury, Brit. M. J. **2**:643-646 (Nov. 28) 1942.

The distal tubular epithelium is severely injured and often necrosed, with formation of foci of exudation and peritubular venocapillary thrombosis resembling "tubulovenous fistulas."[7] The lesion is similar to that which follows intravascular hemolysis from mismatched transfusion, to that of blackwater fever and to that caused by hemoglobinuria in severely burned persons. An analogous lesion may follow administration of sulfonamide drugs.[8]

It thus seems likely that the renal lesion of crush syndrome is a special instance of a generic injury related functionally to renal abnormalities which appear during shock and structurally to many types of nontraumatic renal damage.

The nature and treatment of post-traumatic renal injuries were studied experimentally by investigation of renal function in the following states: (1) hemorrhagic shock, (2) tourniquet shock and (3) simulation of crush syndrome.

HEMORRHAGIC SHOCK

Shock due to hemorrhage was produced in dogs by repeated severe bleeding and transfusion while they were under pentobarbital anesthesia. Protocols of some of these experiments were reported elsewhere in detail.[9] Results of a typical experiment are presented graphically in figure 1.

The first renal changes after severe bleeding result from arterial hypotension. Renal blood flow decreases. The glomerular filtration rate is proportionately more depressed, for filtration requires a higher head of pressure in the glomerular capillaries than is necessary to maintain even a low rate of tissue perfusion. Depression of glomerular filtration results in oliguria, which persists during hypotension.

After a short period of hypotension, rapid restoration of arterial pressure by intra-arterial transfusion[10] brings to normal the rates of renal blood flow and glomerular filtration and is usually accompanied with mild diuresis. However, when, as may commonly occur in practice, hypotension is prolonged beyond forty minutes, when, as in the experiment, bleeding is resumed after transfusion or when transfusion is inadequate, so that hypotension recurs or persists, a more serious change appears. This consists in increased vascular resistance to the flow of blood, so that blood flow, filtration rate and urine flow remain depressed even when normal blood pressure is restored. The increased vascular resistance is not a passive adaptation of vessels to a diminished blood volume but an active vasoconstriction, which is not released by the restora-

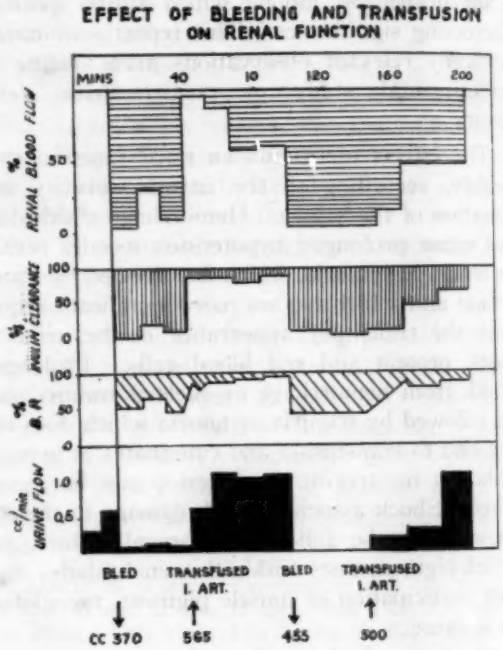

Fig. 1.—Percentage of normal total renal blood flow and inulin clearance (glomerular filtration rate), blood pressure and urine flow in two succeeding phases of hypotension due to bleeding and followed by intra-arterial infusion of blood.

tion to normal of blood volume and arterial pressure. Because of this, delayed transfusion in hypotension due to bleeding does not at once restore renal function and urine flow to normal. In shock from bleeding the presence of renal ischemia may be inferred from the absence of diuresis after apparently adequate transfusion.

Renal function was measured by plasma clearance of diodrast and inulin and, in most instances, concurrent determination of the proportions of these substances removed from the blood during its passage through the kidney (renal extraction ratios). Under normal conditions or in animals

7. Dunn, J. S.; Gillespie, M., and Niven, J. S. F.: Renal Lesions in Two Cases of Crush Syndrome, Lancet **2**:549-552 (Nov. 8) 1941.

8. Maisel, B.; McSwain, B., and Glenn, F.: Lesions Produced with Sulfadiazine, Proc. Soc. Exper. Biol. & Med. **49**:715-717 (April) 1942. Murphy, F. D.; Kuzma, J. F.; Polley, T. Z., and Grill, J.: Clinicopathologic Studies of Renal Damage Due to Sulfonamide Compounds: Report of Fourteen Cases, Arch. Int. Med. **73**:433-443 (June) 1944.

9. Corcoran, A. C., and Page, I. H.: Effects of Hypotension Due to Hemorrhage and of Blood Transfusion on Renal Function in Dogs, J. Exper. Med. **78**:205-224 (Sept.) 1943.

10. Kohlstaedt, K. G., and Page, I. H.: Hemorrhagic Hypotension and Its Treatment by Intra-Arterial and Intravenous Infusion of Blood, Arch. Surg. **47**:178-191 (Aug.) 1943.

anesthetized with pentobarbital,[11] renal extraction ratios for inulin and diodrast remain relatively constant and that for diodrast is so large (about 0.85) that plasma diodrast clearance is the near equivalent of renal plasma flow. However, during severe and prolonged hypotension the renal diodrast extraction ratio is depressed, so that diodrast clearance equals only a fraction (0.5 or even less) of renal plasma flow.

During and immediately after transfusion, diodrast clearance rises rapidly, often to levels exceeding normal. It might be concluded that the kidney responds to hypotensive ischemia by reactive hyperemia. Actually, renal blood flow is usually returned to, or is but little beyond, the normal level and soon falls. The temporary high diodrast clearance level when glomerular filtration is restored apparently results from the washing out of diodrast secreted into the tubules during hypotension. An example has been reported in a case of orthostatic hypotension.[12]

In summary, shock due to prolonged or repeated bleeding depresses renal function by causing a vasoconstrictive ischemia, which is not released by transfusion of blood and restoration to normal of arterial pressure.

The persistence of renal ischemia and anoxia in experimental shock due to bleeding seems to explain the prolonged renal functional depression which may follow bleeding in human beings. Therapeutically, it is significant that renal denervation does not prevent the vasoconstriction; hence there is no experimental basis for the treatment of posthemorrhagic urinary suppression by spinal anesthesia or paravertebral block. The nature of the abnormality makes the use of vasoconstrictor drugs illogical.

TOURNIQUET SHOCK

To mimic more closely the conditions of crush syndrome in human beings, renal function in dogs was studied during the onset of shock resulting from experimental application of tourniquets partially occluding arterial inflow. Details of the experiments have been reported elsewhere.[13]

The sequence of renal vascular changes (fig. 2) contrasts in some respects with that of the changes which follow bleeding. Arterial pressure is well maintained and even at first increased. In spite of this, renal blood flow decreases by about 20 per cent during the first fifteen minutes, by 50 per cent in thirty minutes and by 80 per cent in sixty to one hundred minutes after application of the tourniquet. Decreased renal blood flow without concomitant decrease in arterial pressure can result only from increased resistance to the flow of blood through the kidneys, brought about presumably by renal vasoconstriction. The glomerular filtration rate, measured as inulin clearance, is less decreased

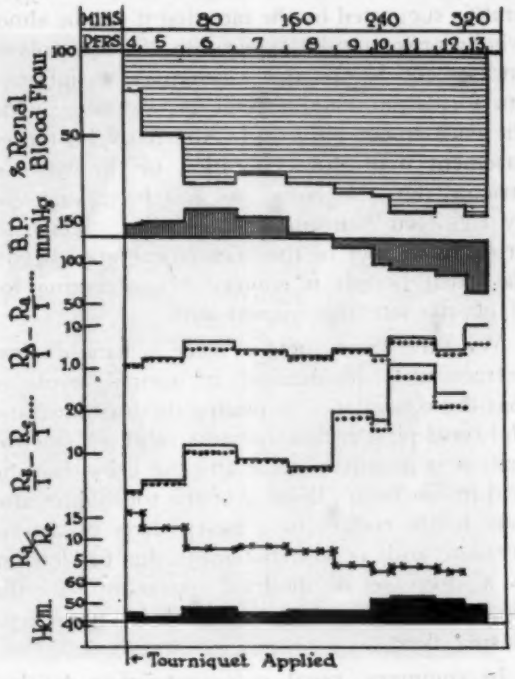

Fig. 2.—Percentage of normal total renal blood flow, blood pressure, hematocrit reading *(Hem.)*, and concurrent changes in glomerular arteriolar afferent (R_A and R_a) and efferent (R_E and R_e) resistance during the onset of shock due to application of tourniquets to the limbs.

than is the rate of blood or plasma flow. The partial maintenance of glomerular filtration is due to an increase in intraglomerular pressure. Analysis of these changes according to formulas suggested by Lamport [14] indicates that the increase of intraglomerular pressure is due to predominance of constriction in the glomerular efferent arterioles, so that the function R_E (re-

11. Corcoran, A. C., and Page, I. H.: Effects of Anesthetic Dosage of Pentobarbital Sodium on Renal Function and Blood Pressure in Dogs, Am. J. Physiol. **140**:234-239 (Nov.) 1943.

12. Corcoran, A. C.; Browning, J., and Page, I. H.: Renal Hemodynamics in Orthostatic Hypotension: Effects of Angiotonin and Head-Up Bed, J. A. M. A. **119**:793-794 (July 4) 1942.

13. Corcoran, A. C.; Taylor, R. D., and Page, I. H.: Immediate Effects on Renal Function of the Onset of Shock Due to Partially Occluding Limb Tourniquets, Ann. Surg. **118**:871-876 (Nov.) 1943.

14. Lamport, H. J.: Improvements in Calculation of Renal Resistance to Blood Flow: Charts for Osmotic Pressure and Vicosity of Blood, J. Clin. Investigation **22**:461-470 (May) 1943.

sistance distal to the glomerulus) is greater than R_A (resistance proximal to the glomerulus) (fig. 2).

This vasoconstriction is only partially relieved by interruption of vasomotor impulses, restoration of blood volume or prevention of hemoconcentration, for renal blood flow remains reduced by half even after transfusion, splenectomy [15] and renal denervation.

That this vasoconstriction, like that which follows prolonged or repeated bleeding, is of humoral origin is supported by the appearance in the plasma of a vasoconstrictor substance [16] soon after application of the tourniquet. The nature, site and mode of release of the substance are not known. That it originates in the injured limb is suggested by the fact that it can be almost wholly prevented by application of a snug plaster encasement before the tourniquet is tightened. Its formation may depend on swelling, which the encasement prevents. Alternatively, the encasement may slow liberation of the vasoconstrictor into the blood, as has been suggested by Eggleton [17] in analogous studies. Thus, the protective effect of the encasement goes beyond the great benefit it confers by preventing loss of plasma into the injured limb.[18]

With the tourniquets in place, plasma diodrast extraction is maintained at normal levels, so that the equivalence of plasma diodrast clearance and renal plasma flow remains valid. Urine formation is greatly slowed, and the urine becomes acid in reaction. Release of the tourniquet after four hours results in a sharp drop of arterial pressure and, as in hypotension due to bleeding, in a decrease of diodrast extraction, so that diodrast clearance becomes much less than renal plasma flow.

In summary, renal vasoconstriction develops more rapidly and more severely during the onset of shock due to skeletal trauma than in shock due to bleeding, in which tissue damage is milder and more diffuse. It cannot readily be established from experiments on dogs that vasoconstriction is an adequate explanation of posttraumatic anuria, for in dogs trauma from tourniquets sufficient to cause severe vasoconstriction causes death within a few hours whereas lesser degrees of trauma are followed by systemic and renal recovery. Clinical evidence suggests that, in contrast to dogs, human beings may survive the state of shock without recovery of renal function, possibly because their renal vessels are more sensitive than those of dogs to vasoconstriction in trauma. In this connection Lauson, Bradley and Cournand [19] showed that in human beings in shock the degree of renal vasoconstriction exceeds that of the rest of the arterial tree.

EXPERIMENTAL CRUSH SYNDROME

The first step in the study of crush syndrome lay in delimiting the effects of myoglobinuria on renal function. Details of this study will be reported elsewhere.[19a]

The molecular weight of myoglobin is one-fourth that of hemoglobin. It is therefore passed through glomerular capillaries about twenty-five times as rapidly as hemoglobin at equivalent plasma concentrations.[20] The pigment is not long retained in plasma. The possibility of its causing renal injury is a priori greater than that of hemoglobin when the physiochemical conditions of distal tubular urine are conducive to precipitation of either pigment.

Instances of severe renal injury from injection of human myoglobin into rabbits with acid urine were observed by Bywaters and Stead.[21] However, in our experience, the renal injury caused by injection of beef metamyoglobin [22] in dogs with acid urine, although a constant occurrence, was not usually sufficiently severe to simulate that of crush syndrome. In contrast,

15. Taylor, R. D., and Page, I. H.: Mechanism of Erythremia: Erythremia Resulting from Traumatic Shock in Dogs and from Injections of Epinephrine into Human Beings and Dogs, Arch. Surg. **47**:59-68 (July) 1943.

16. Page, I. H.: Occurrence of a Vasoconstrictor Substance in Blood During Shock Induced by Trauma, Hemorrhage, and Burns, Am. J. Physiol. **139**:386-398 (July) 1943.

17. Eggleton, M. G.: Crush Kidney Syndrome in the Cat, Lancet **2**:208-210 (Aug. 12) 1944.

18. Duncan, G. W., and Blalock, A.: The Uniform Production of Experimental Shock by Crush Injury: Possible Relationship to Clinical Crush Syndrome, Ann. Surg. **115**:684-697 (April) 1942.

19. Lauson, H. D.; Bradley, S. E., and Cournand, A.: Renal Circulation in Shock, J. Clin. Investigation **23**:381-402 (May) 1944.

19a. Texas Rep. Biol. & Med., to be published.

20. Yuile, C. L., and Clark, W. F.: Myohemoglobinuria: Study of Renal Clearance of Myohemoglobin in Dogs, J. Exper. Med. **74**:187-196 (Sept.) 1941.

21. Bywaters, E. G. L., and Stead, J. K.: The Production of Renal Failure Following Injection of Solutions Containing Myohemoglobin, Quart. J. Exper. Physiol. **33**:53-70 (Sept.) 1944.

22. The metamyoglobin was prepared by Dr. O. M. Helmer from beef hearts, by the method of Theorell. (Theorell, A. H. T.: Kristallinisches Myoglobin; Kristallisieren und Reinigung des Myoglobins sowie vorläufige Mitteilung über sein Molekulargewicht, Biochem. Ztschr. **252**:1-7, 1932.) The preparation contained a nondiffusible nitrogenous contaminant, presumably an albumin, which accounted for 10 to 20 per cent of its weight.

Bing [23] did not observe renal injury in acidotic dogs given dog myoglobin but obtained severe injury from injections of dog methemoglobin.

The basis of renal damage caused by the pigment lay in its deposition within the renal tubules. Since the extent of injury sometimes progressed for several days after myoglobinuria had ceased, the existence of a tubular cytotoxic as well as a mechanical obstructive injury was assumed. In contrast with earlier observations [24] which suggested that hemoglobin—and, by inference, myoglobin—causes renal ischemia, the injection of either dog hemoglobin or beef metamyoglobin either did not change renal blood flow or caused brief renal hyperemia. Addition to the metamyoglobin of other muscle extractives did not increase renal injury beyond that expected from injection of pigment alone.

The severe renal damage of crush syndrome seemed, therefore, to depend on the combination of renal damage from trauma and that caused by the pigment. Both post-traumatic renal ischemia and myoglobinuria were then produced in dogs by application of a tourniquet and injection of myoglobin. In these experiments, as in those in which no myoglobin was given, trauma severe enough to cause severe renal ischemia was followed by death within twenty-four hours, whereas minor trauma was followed by recovery, with no more injury than might be caused by injection of metamyoglobin in a normal dog with acid urine.

Since the problem could not be easily investigated in dogs, rats were substituted. In that species, trauma and consequent renal functional injury could be extremely severe without causing early death in shock. Another advantage is that rats, like rabbits,[25] have little myoglobin in limb muscles. Therefore, a comparison between the effects of trauma to rat muscle without injection of metamyoglobin with trauma to rat muscle with injection of metamyoglobin permits an evaluation of the degree to which the pigment may participate in crush syndrome in human beings, whose muscles contain myoglobin.

Experiments were conducted with the animals under pentobarbital anesthesia. One clipped hindleg was spirally wrapped from the toes upward with stout cord under firm tension (fig. 3). The cord was removed at the end of five hours, restoring blood flow. The limb swelled and later became firm and indurated with exudate. Muscles showed patchy fragmentation with loss of striation of the fibers and foci of exudate in the edematous interstitial tissues. The arterial pressure [26] was maintained until the cord was released. One hour after release of the cord the arterial pressure was about 70 mm. of mercury. At this time the blood hemoglobin level was increased as a result of hemoconcentration, and creatine and phosphate appeared in the plasma in excessive amounts. The plasma carbon dioxide content was not depressed. The femoral vein was then exposed, and 1 cc. of 0.9 per cent solution of sodium chloride was injected into the animals of one group and 1 cc. of 0.9 per cent solution of sodium chloride containing 0.1 mg. of beef metamyoglobin per gram of body weight was injected into the others. Since the injection caused arterial pressure to rise to 90 to 100 mm. of mercury, about 1 cc.

Fig. 3.—Appearance of rat's crushed limb (*A*) after application of the cord and (*B*) five minutes, (*C*) one hour and (*D*) twenty-four hours after release of cord.

23. Bing, R. J.: Effect of Hemoglobin and Related Pigments on Renal Function of Normal and Acidotic Dog, Bull. Johns Hopkins Hosp. **74**:161-176 (March) 1944.

24. Mason, J. B., and Mann, F. C.: Effect of Hemoglobin on Volume of Kidney, Am. J. Physiol. **98**:181 (Sept.) 1931. Hesse, E., and Filatov, A.: Experimentelle Untersuchungen über das Wesen des hämolytischen Schocks bei der Bluttransfusion und die therapeutische Beeinflussung desselben; die Nierenfunktionsstörungen im akuten Experiment, Ztschr. f. d. ges. exper. Med. **86**:211-230, 1933.

25. Bywaters, E. G. L., and Popjak, G.: Experimental Crushing Injury: Peripheral Circulatory Collapse and Other Effects of Muscle Necrosis in Rabbit, Surg., Gynec. & Obst. **75**:612-627 (Nov.) 1942.

26. Measurements were made by Dr. G. F. Kempf.

of blood was withdrawn to maintain the pressure at 70 mm. of mercury. The small loss of blood, equivalent to about 10 per cent of the blood volume, does not explain the severe anemia which appeared in crushed rats (fig. 4). Similar anemia has been observed to follow trauma in human beings as hemoconcentration recedes. Our data do not indicate that it is related to the concomitant renal injury.

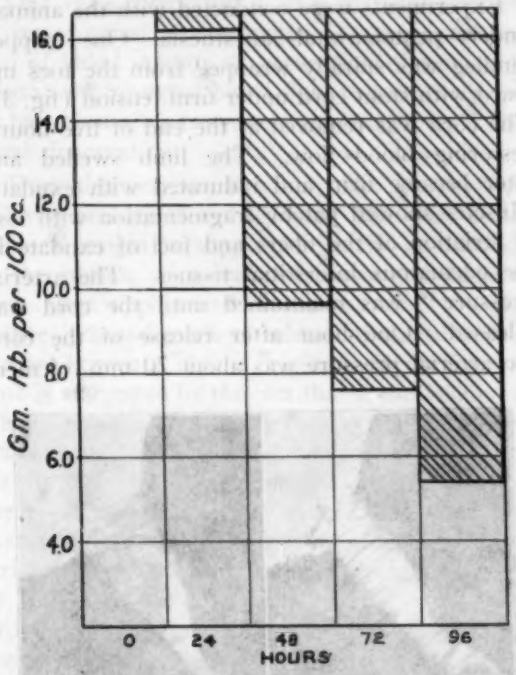

Fig. 4.—Mean blood hemoglobin content (normal control 16.6 Gm. per hundred cubic centimeters) in crushed myoglobin-treated rats at twenty-four hour intervals after injury.

Participation of Myoglobin.—A state comparable to that found in human beings with crushed limbs was thus experimentally established. The participation of muscle pigment in the renal injury of crush syndrome was examined by comparing on succeeding days the levels of blood urea nitrogen and the rates of mortality in crushed rats given injections of isotonic solution of sodium chloride and those given metamyoglobin in isotonic solution of sodium chloride. Renal structural changes were also compared.[27]

The degree of azotemia varied widely in the myoglobin-treated and the sodium chloride-treated groups. That in the sodium chloride-treated group was attributed to the combination of renal vasoconstrictive functional depression and increased nitrogen destruction. Minor nonspecific renal structural changes were present in these animals (fig. 6). The mean levels of blood urea nitrogen were higher in the group treated with metamyoglobin. The difference is statistically significant (difference/standard error of the difference > than 3)[28] at twenty-four, forty-eight and seventy-two hours after crushing. Thereafter, the difference between the means of the two groups disappears because of the high

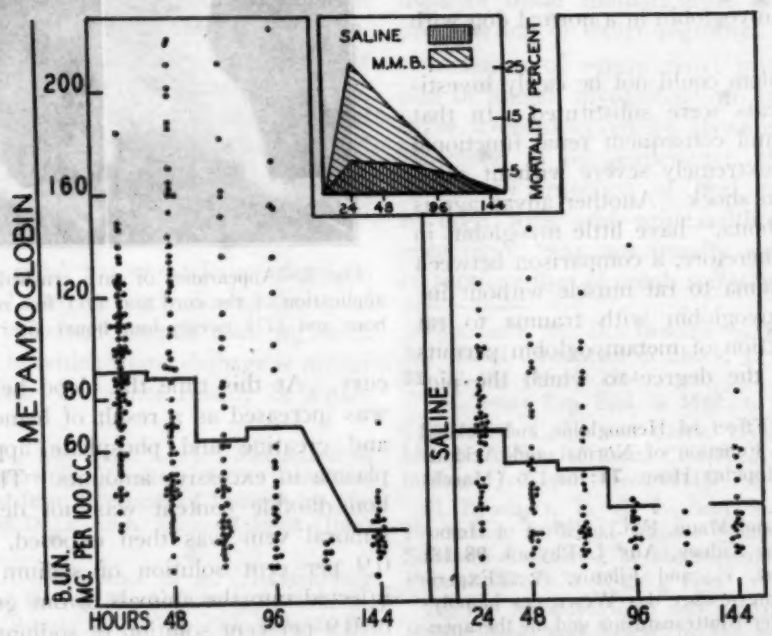

Fig. 5.—Individual and mean values of blood urea nitrogen and (insert) mortality percentage in crushed rats given metamyoglobin and those given an equal volume of 0.9 per cent solution of sodium chloride.

27. Examinations were made by Dr. Paul N. Harris.

28. Hill, A. B.: Principles of Medical Statistics, London, The Lancet, 1942.

death rate of those myoglobin-treated animals with severe renal injury and great azotemia.

Structural changes in the kidneys of the metamyoglobin-treated rats were more severe in all categories of injury than in those given injections of isotonic solution of sodium chloride. Pigment casts and necrosis of all the distal tubules, such as appear in the crush syndrome in human beings, were present only in the myoglobin-treated animals.

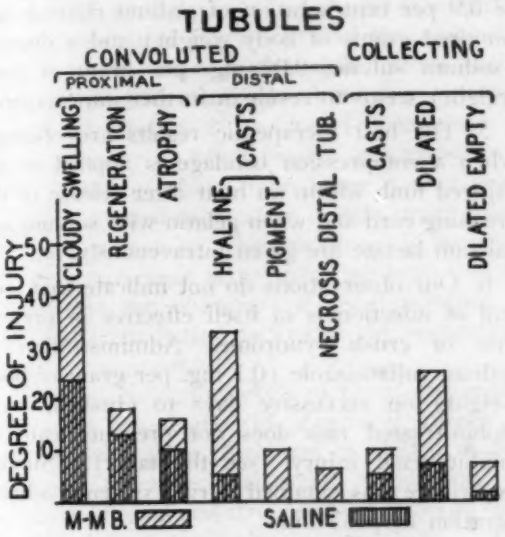

Fig. 6.—Summary of site and character of renal structural change in crushed rats treated with metamyoglobin (M-MB) and those given an equal volume of 0.9 per cent solution of sodium chloride. Structural changes were graded 1 to 4 plus, an arbitrary figure of 25 assigned to 1 plus, and the results averaged.

Thus, from the aspects of azotemia, mortality and structural renal changes, the combination of crushing injury to skeletal muscles and injection of metamyoglobin into rats is shown to result in a state comparable to crush syndrome in human beings. Renal damage apparently is produced in human beings by a combination of vasoconstrictive ischemia, oliguria and aciduria, with the deposition in the kidneys of the muscle pigment, myoglobin. The state experimentally produced lends itself to the study of methods of clinical treatment.

Treatment.—Pertinent here is a brief selection of observations of immediate clinical significance. Some of the relevant data are presented in the table. From the point of view of treatment, the conditions of the experiments may be divided into those which (*a*) adversely and (*b*) favorably affect the outcome from the aspects of renal injury (azotemia) and mortality.

Adverse Conditions.—1. Dehydration by deprivation of water before crushing or by high environmental temperature (around 85 F.) results in increased renal injury and mortality. Gangrene of the injured limb is common when external temperatures are high and rare under conditions of moderate temperature. Parenteral administration of fluid as 0.9 per cent solution of sodium chloride to severely dehydrated animals after crushing and injection of metamyoglobin has little beneficial effect.

2. Injection of a large dose of a diuretic, such as 0.1 mg. of sodium sulfate per gram of body weight, increases immediate mortality, apparently by intensifying shock.

3. Intravenous injection of sodium citrate has been recommended in the early treatment of crush syndrome. Given in a dose of 0.1 mg. per gram of body weight, which is equivalent roughly to a dose of 5 Gm. for a human being, sodium citrate causes severe tetany, which is sometimes immediately fatal or which, by intensifying shock, greatly increases mortality during the first twenty-four hours. Survivors show no significant reduction in the degree of renal injury. The susceptibility to tetany of crushed animals treated with sodium citrate is ascribed to the

Effects of Treatment in Experimental Crush Syndrome *

Group	Animals, Number	24 Hours: Blood Urea Nitrogen, Mg. per 100 Cc.	24 Hours: Death, Percentage	48 Hours: Blood Urea Nitrogen, Mg. per 100 Cc.	48 Hours: Death, Percentage	72 Hours: Blood Urea Nitrogen, Mg. per 100 Cc.	72 Hours: Death, Percentage
Sodium chloride control	47	66	6	52	5	51	2
Myoglobin control	96	90	25	89	15	64	4
Myoglobin-treated							
Sodium citrate	26	101	70	96	28	70	20
Sodium sulfathiazole	24	79	19	67	23	60	0
Diuresis, moderate	48	66	31	49	11	40	0
Gelatin	48	72	2	58	11	54	10
Gelatin lactate	24	65	6	43	10	33	11
Pressure bandage	22	79	0	52	0	56	0
Pressure bandage with diuresis	24	49	4	30	8	23	0
Pressure bandage with gelatin lactate	23	35	9	23	9	19	0

* Summary of mean levels of blood urea nitrogen and mortality per cent in control series given injections of isotonic solution of sodium chloride and myoglobin and in crushed rats given injections of myoglobin receiving various types of treatment.

presence of hyperphosphatemia. Intravenous administration of calcium lactate relieves the tetany, but in the absence of a demonstrable beneficial effect of injection of citrate on renal injury there does not seem to be a sound basis for its use. The toxic action of citrate in shock due to muscle crush is of significance, since a dangerous dose of citrate may be unintentionally given during rapid transfusion of a liter of citrated plasma.

4. Although not so immediately toxic as citrate, sodium bicarbonate, in a dose of 0.1 mg. per gram of body weight, is equally ineffective in preventing renal injury.

Experimentally, treatment or prevention of crush syndrome by alkalinization alone does not seem to be justified and may be dangerous. The danger of dependence on alkalis in an analogous state, blackwater fever, was recently emphasized by Maegraith and Havard.[29]

Favorable Conditions. — 1. Maintenance of normal hydration before injury and of moderate external temperature afterward ameliorates both renal injury and mortality.

2. Diuretics in moderate doses intravenously (mannitol or sucrose, 0.1 mg. per gram of body weight, sodium sulfate 0.02 mg. per gram of body weight) reduce the degree of renal injury as measured by blood urea nitrogen levels and histologic study but do not significantly affect mortality.

3. Intravenous injection of a 4 per cent solution of gelatin (1.5 cc. per hundred grams of body weight) decreases the degree of functional and structural renal injury and reduces mortality. Gelatin seemed somewhat more effective in a sixth-molar solution of sodium lactate than in a 0.9 per cent solution of sodium chloride. Addition of calcium lactate (0.02 mg. per gram of body weight) to the solution seems to improve the tolerance of crushed animals to rapid intravenous injection of gelatin, but no more definite benefit can be ascribed to this addition.

4. Application of a compression bandage to the injured limb was advocated early in the clinical study of crush syndrome by Patey and Robertson,[30] who considered that renal injury might result solely from oligemia and that compression would prevent it by restricting the loss of plasma. However, beneficial effects of compression of limb in shock due to muscle trauma may also be attributed to prevention of vasoconstrictive renal ischemia and the attendant changes which render the kidney susceptible to injury from deposition of myoglobin. Decreased mortality and less evidence of renal injury are found in crushed metamyoglobin-treated rats when an elastic compression bandage is applied to the limb either immediately or one hour after release of the compression. Injection of fluid (1.5 cc. of 0.9 per cent solution of sodium chloride per hundred grams of body weight) and a diuretic (sodium sulfate, 0.02 mg. per gram of body weight) seems to result in further improvement.

5. The best therapeutic results are obtained when a compression bandage is applied to the injured limb within an hour after release of the crushing cord and when gelatin with sodium and calcium lactate are given intravenously.

6. Our observations do not indicate that control of infection is of itself effective in prevention of crush syndrome. Administration of sodium sulfathiazole (0.1 mg. per gram of body weight) on successive days to crushed, myoglobin-treated rats does not prevent death or inhibit renal injury (see the table). Similar experience was obtained during systemic administration of penicillin.

COMMENT

In shock, whether due to bleeding or to skeletal injury, renal vasoconstriction occurs. This vasoconstriction is apparently caused by a substance released from the site of tissue damage. The vasoconstriction and the resultant oliguria occur rapidly when shock is induced by skeletal trauma but may be present in severe degree in the terminal stages of shock due to hemorrhage. Thus, the common denominator of renal injury from shock due to trauma is renal ischemia. A severe form of renal ischemia may cause in human beings irreversible renal injury of the type obtained by Phillips and Van Slyke[31] and Scarff and Keele[32] after prolonged occlusion of renal arteries by clamps. To this mechanism may be ascribed the late deaths in anuria which result from prolonged shock without myoglobinuria or hemoglobinuria.

Theoretically, vasoconstriction in shock is an indication for the use of renal vasodilators. Practically, their use in unpublished experiments has not been rewarding, possibly because proper timing of administration and the necessary con-

29. Maegraith, B. G., and Havard, R. E.: Dangers of Intensive Alkali Treatment in Blackwater Fever, Lancet **2**:338-339 (Sept. 9) 1944.

30. Patey, D. H., and Robertson, J. D.: Compression Treatment of Crush Injuries of Limbs, Lancet **1**:780-782 (June 21) 1941.

31. Phillips, R. D., and Van Slyke, P. D.: Personal communication to the authors, 1943.

32. Scarff, R. W., and Keele, C. A.: Effects of Temporary Occlusion of Renal Circulation in Rabbits, Brit. J. Exper. Path. **24**:147-149 (Aug.) 1943.

comitant restoration of arterial pressure and blood volume have not been determined.

Before renal vasoconstriction develops to the degree which of itself may cause renal failure, the kidney is predisposed to injury by deposition of such pigments as myoglobin, released into the circulation as blood flow is reestablished in severely damaged muscle tissue. This explanation of the genesis of crush syndrome is in agreement with that of Bywaters [6] and Bywaters and Stead.[21] Our observations differ from theirs more in emphasis than in kind, for they observed severe renal injury more often (fifteen times in 25 experiments) when human myoglobin was given aciduric rabbits than when it was given rabbits subjected to standard muscle crush (twice in 6 experiments). Their emphasis is therefore on the significance of aciduria, while to this we would add the oliguria and renal ischemia of shock as contributing factors to the nephrotoxic action of pigment.

Comparison of the levels of blood urea nitrogen with the degree of structural change in crushed rats given injections of metamyoglobin shows a general correlation. A disparity between functional and structural estimates of damage is present in individual instances. This disparity may support the supposition that renal injury in crush syndrome is of multiple origin —namely, ischemic, hydronephrotic (from tubular block) and nephrotoxic (from damage to tubular cells). This ischemic factor is treated prophylactically by compression bandaging and intravenous infusion of fluid as a plasma-like colloid.

The mechanism and treatment of the presumptive toxic element are not clear. It is supposed that the injury to the cells, especially of the distal convoluted tubule, common to hemolytic transfusion reactions, blackwater fever, burns and crush syndrome, is due to intratubular and intracellular release of hematin. Hematin is released from the heme-globin linkage during the extravascular breakdown of ferri-hemeglobin pigments, such as metamyoglobin or methemoglobin.[33] Prevention of toxic injury might thus rest on the prevention (*a*) of oxidation of hemoglobin or myoglobin to their meta forms or (*b*) of the enzymatic breakdown of methemoglobin or metamyoglobin. However, as regards the first possibility, administration of reducing substances, such as sodium thiosulfate, which might prevent oxidation of myoglobin to the meta form, did not protect against renal injury in experiments in which metamyoglobin was given intravenously. Thus the prevention of tubular injury due to cellular necrosis as well as that due to hydronephrotic obstruction still rests on preventing deposition of pigment.

The prevention of deposition of pigment is accomplished by reversing the conditions, oliguria and aciduria,[34] which favor it. The treatment of shock by transfusions and pressure bandages inhibits the renal vasoconstriction on which oliguria may depend. A free flow of urine may occur during the reestablishment of blood volume by transfusion, and when this is not achieved or maintained gelatin may be added to an infusion of sodium lactate containing calcium lactate, since gelatin is itself mildly diuretic.[35] A small dose of another diuretic, such as sodium sulfate, may be given. However, the dangers and the ineffectiveness of alkalinization by injection of citrate as the sole means of treatment have been pointed out.

CONCLUSIONS

1. Renal vasoconstriction of humoral origin, apparently arising in damaged tissue, occurs in shock, whether caused by bleeding or by skeletal injury.

2. When sufficiently prolonged such vasoconstriction and its consequent anuria may persist in spite of restoration of blood volume and blood pressure.

3. Renal ischemia and oliguria, which of themselves might be inadequate to cause renal failure, predispose to the intrarenal precipitation of myoglobin, which leads to renal failure of the type known as crush syndrome.

4. The treatment of crush syndrome is prophylactic and rests on the prevention of renal ischemia and of deposition of pigment.

Mr. Truman Woodmansee, B. S., assisted the authors in this work.

33. It may be for this reason that injected methemoglobin is more injurious to renal function than equal doses of hemoglobin in the ferrous forms.[23]

34. Yorke, W., and Nauss, R. W.: The Mechanism of the Production of Suppression of Urine in Blackwater Fever, Ann. Trop. Med. & Parasitol. **5**:287-312, 1911. Baker, S. L., and Dodds, E. E.: Obstruction of the Renal Tubules During the Excretion of Haemoglobin, Brit. J. Exper. Path. **6**:247-260 (Oct.) 1925. Bywaters and Stead, footnote 21.

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CHRONIC ULCERATIVE COLITIS WITH GENERALIZED PERITONITIS AND RECOVERY

TREATMENT WITH PENICILLIN AND SULFADIAZINE

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Perforation of the colon is a rather uncommon complication of ulcerative colitis. Bargen,[1] in a series of 693 cases of ulcerative colitis with two hundred and sixty-eight complications of various types, found perforation fifth in order of frequency. Bargen and Jacobs[2] reported twenty-two perforations (3.4 per cent) in 647 cases. Jackman, Bargen and Helmholz[3] found two perforations in 95 cases of ulcerative colitis in children (2 per cent) and sixteen in the total group of 871 cases (1.1 per cent). As nearly as can be judged from the literature, free perforation of the colon with generalized peritonitis has hitherto been a fatal occurrence. Chronic perforation with abscess formation, on the other hand, is not infrequently followed by recovery. The purpose of this paper is to report 3 cases of what was considered to be perforation of the colon with generalized peritonitis successfully treated with sulfonamide drugs and penicillin and, in 1 case, subsequent surgical drainage of localized collections of pus.

REPORT OF CASES

CASE 1.—A 41 year old white stenographer enjoyed good health until July 1939, when she experienced an episode of diarrhea consisting of four to six loose stools daily for one week. After this episode she felt well until the diarrhea recurred one month later accompanied with abdominal distress relieved by passing flatus. The diarrhea persisted with remissions and exacerbations until January 1941, when it increased to as many as twenty bloody stools daily. After careful examination, including proctoscopy, a diagnosis of chronic ulcerative colitis was made,[4] and later confirmed at Mayo Clinic. With medical treatment, including blood transfusions, the patient gained considerably, although she continued to experience recurrent exacerbations of diarrhea. A definite correlation was noticed between the increased number of stools and the number of "colds or nervous upsets."[4]

On May 1, 1944, during a period of diarrhea, an acute pain appeared in the right upper quadrant of the abdomen, radiating to the right lower quadrant, accompanied with vomiting and fever. The patient arrived at the Rockford Hospital, Rockford, Ill., at 5:30 p. m. with a temperature of 99.8 F., a pulse rate of 96, an erythrocyte count of 4,240,000, a hemoglobin content of 13 Gm. and a white blood cell count of 18,550, with 91 per cent granulocytes, of which 22 per cent were not filamented. The following morning the abdomen was rigid, and the white blood cell count rose to 21,150, with 92 per cent granulocytes and 14 per cent nonfilamented forms. Culture of stools revealed Staphylococcus aureus and Escherichia coli. The following morning, May 3, the temperature was 100.2 F., the pulse rate 120 and the respiration rate 16. In addition to intravenous injections of dextrous and isotonic solution of sodium chloride, the patient received a transfusion of 400 cc. of whole blood. Penicillin, 30,000 units, was given on May 3, but its use could not be continued because no more was available. The following morning the patient was given 5 Gm. of sulfamerazine and 1,000 cc. of isotonic solution of sodium chloride intravenously. The use of the drug was continued at intervals with the intravenous injections of fluids, a blood level of about 4.5 mg. per hundred cubic centimeters being maintained. An additional transfusion was given on May 8. Adequate fluids were given to maintain a urinary concentration from 1.007 to 1.012. Water was given by mouth on May 5; on May 6 a low residue liquid diet was allowed. On May 7 the oral administration of sulfamerazine was instituted, 1 Gm. being given every six hours. On May 9 this was reduced to 1 Gm. every eight hours and continued through May 13, at which time the administration of sulfaguanidine was begun, a rather small dose of 4 tablets being used every six hours. The following day there was a questionable cutaneous reaction to the sulfguanidine, and, because there had been some question of reaction to this drug in the past, it was changed to succinylsulfathiazole, which was continued until she was removed from the Rockford Hospital to the Albert Merritt Billings Hospital on May 16.

Physical examination at that time disclosed a well developed, somewhat undernourished, acutely ill patient with a blood pressure of 110 systolic and 75 diastolic, a pulse rate of 90 and a temperature of 101.4 F. The abdominal wall was slightly tense, with moderate tenderness and muscular resistance in the lower part of the abdomen, where a tender mass with rather indefinite borders extending from the symphysis pubis almost to the umbilicus could be made out. A pronounced

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

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leukocytosis was present. The patient took food and fluids rather poorly by mouth, and hence from June 1 to June 8 she received 2,000 cc. of amigen with 5 per cent dextrose intravenously daily. From June 4 to 8 penicillin was given in a daily dose of 240,000 units; no sulfonamide drug was administered.

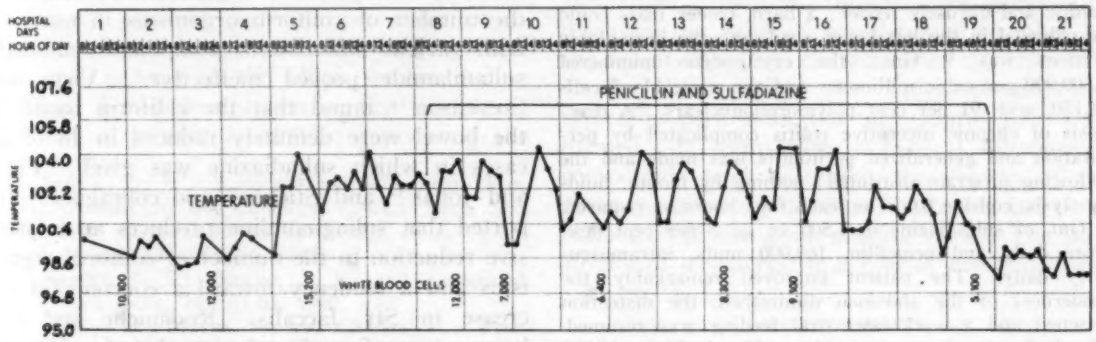
On May 23, 1944 Dr. William Adams made a 3 inch (7.6 cm.) incision 3 inches above the pelvis and extending to the umbilicus to drain the huge abscess filling the lower part of the abdomen. Green pus poured out under pressure. One Penrose drain was inserted and a dressing applied. Microscopic examination of two small hemorrhagic bits of tissue showed an extensive infiltration of inflammatory cells. The postoperative course was stormy, with a temperature ranging from 100 to 104 F. The diarrhea continued. The abscess drained freely. Anorexia persisted with occasional emesis. On June 22, 1944 a large abscess was found over the ninth, tenth and eleventh ribs on the right side. It was drained, 100 cc. of bloody, "tomato juice-like" purulent material being obtained. Culture disclosed Streptococcus viridans and Esch. coli.

The patient improved considerably. A roentgen ray examination of the colon on July 5 was reported as showing an old chronic ulcerative colitis involving the entire colon, with pronounced narrowing of the sigmoid flexure and with two fistulous tracts, one connecting with the cecum and the other probably with the hepatic flexure. The patient was discharged on July 20, 1944 and advised to return in two months for an ileostomy.

Case 2.—A 35 year old white housewife dated the onset of her present disease back to 1933, when she had had an attack of "colitis" with innumerable liquid, bloody and mucous stools, a distressing "feeling of gas," painful cramps and discomfort in the abdomen. This syndrome recurred at intervals for a number of years. In 1941, when she was in Mexico, diarrhea developed again; the stools were examined on her return, and Endamoeba histolytica was found on two occasions. Treatment with emetine and vioform was followed by complete relief of symptoms. In May 1943 she experienced diarrhea, attributed to a food poisoning. After three weeks in a local hospital with no improvement, she entered Mayo Clinic in June, where Dr. Bargen confirmed the diagnosis of nonspecific ulcerative colitis. Repeated analyses of stools for E. histolytica were negative. Under treatment with azosulfamide, vaccine and a diet she improved remarkably.

In July 1944 she was referred to the University Clinics by her psychoanalyst for a routine examination. The bowel function was normal. The physical findings were essentially negative. Proctoscopic examination disclosed only a slight granularity and scarring of the rectal mucosa; it was not friable; no ulcers were seen. Roentgenograms of the gastrointestinal tract were normal. The stools were free from occult blood by the benzidine test; parasites were not found.

In September the patient went on a strenuous vacation, contracted a bad cold, became fatigued and also reached a critical point in the psychoanalysis she was undergoing. The diarrhea recurred and persisted, requiring hospitalization on October 20. The stools were watery, not bloody, eight or nine per day. The temperature varied between 98.6 and 99.7 F. The blood picture was normal. A proctoscopic examination showed the friable granular bleeding mucosa typical of chronic ulcerative colitis. On October 23 the patient was awakened at 2 a. m. with nausea and cramping abdominal pain. The only physical abnormality that could be detected was an area of tenderness about the umbilicus and in the epigastrium, just to the right of the midline. The temperature rose to 102 and 104 F. and remained high (see chart). The patient grew worse rather rapidly in the following days; the abdomen became distended and tender; the face was pinched; the appearance was that of acute toxemia; the white blood cell count was 15,200. Fluids were given by clysis. On October 26 the administration of sulfadiazine and penicillin was begun, 5.75 Gm. of sulfadiazine in 500 cc. of isotonic solution of sodium chloride being given each day together with 100,000 units of penicillin by intramuscular injection, and increased on October 30 to 160,000 units. A transfusion of 500 cc. of whole blood was given on October 26 and 500 cc. of plasma the next day. A Miller-Abbott tube was passed, without relief of the abdominal distention. The pulse rate oscillated between 100 and 136 and the temperature between 101 and 104 F.; the abdomen was extremely distended. On November 4 the substitution of a Wangensteen tube for the obstructed Miller-Abbott tube resulted in the aspiration of a large amount of gas and fluid and greatly relieved the abdominal distention. This procedure was continued through the following days; the general aspect of the patient improved, and the temperature gradually dropped to normal. On November 6, because of the appearance of a rash, the use of penicillin and sulfadiazine was discontinued, a total dose of 1,580,000 units of penicillin and 41.25 Gm. of sulfadiazine having been given. Subsequent recovery was uneventful except for the annoying complication of a recurrent iridocyclitis.



Temperature curve of case 2. The light line indicates the period of administration of penicillin and sulfadiazine.

Case 3.—A 48 year old white grandmother came to the Albert Merritt Billings Hospital April 1, 1944, stating that for at least thirteen years she had had episodes of bloody diarrhea and abdominal cramps

diagnosed as "chronic ulcerative colitis." Usually there had been only three or four loose stools daily, but there had been periods in which the stools were extremely numerous. The physical examination disclosed a small, thin woman with a pinched, lined face, giving an appearance of an age much older than that stated. The descending colon was palpable but not tender. A rectal stricture was found on digital examination. It was possible to introduce the small proctoscope into this stricture. The mucosa was friable and granular, bleeding easily; two or three small polyps were seen, removed and found on histologic study to be papillomas. A barium sulfate enema disclosed the tubelike appearance of the entire colon typical of chronic ulcerative colitis. The stools contained occult blood, but no parasites were found. The blood counts were normal.

On March 8, 1945 the patient was brought to the hospital acutely ill, with the history that for the past two days she had experienced a rather severe stabbing, knifelike pain in the right upper quadrant of the abdomen radiating to the right flank, present almost all the time though more intense occasionally; nausea and vomiting had occurred; the number of the stools had increased. The patient appeared extremely ill; the blood pressure was 100 systolic and 64 diastolic, the pulse rate 130, the respiratory rate 24 and the temperature 101.5 F.; the abdomen was distended, tympanitic and diffusely tender; a hard, tender mass could be palpated in the left lower quadrant; the hemoglobin content was 9 Gm.; the erythrocytes numbered 4,500,000 per cubic millimeter and the white blood cells 21,150, with 91 per cent polymorphonuclears. A diagnosis of chronic ulcerative colitis complicated by perforation and generalized peritonitis was made and the following program instituted: nothing by mouth, fluids by clysis, codeine 0.06 Gm. each four hours as required, 5 Gm. of sulfadiazine in 1,500 cc. of 5 per cent dextrose daily and penicillin, 160,000 units, intramuscularly daily. The patient improved remarkably, the tenderness of the abdomen diminished, the distention lessened and a week later oral feeding was resumed. The leukocyte count dropped on March 19 to 10,800 white cells. On that day the administration of sulfadiazine was stopped, the use of penicillin being continued until April 11.

After the abdominal pain and distention had disappeared, the hard, nontender mass in the left lower quadrant persisted and was interpreted as a carcinoma of the sigmoid developing in a patient with ulcerative colitis. Hence operation was advised in the hope that ileostomy could be performed, followed by complete colectomy later. Dr. Lester Dragstedt, operating on the patient March 28, found the intestines everywhere injected and covered with recent adhesions, thus confirming the clinical diagnosis of generalized peritonitis with recovery.

COMMENT

The normal and the diseased colon contain a rich bacterial flora. Gram-negative bacilli, especially E. coli, predominate; large numbers of cocci are present, chiefly Streptococcus faecalis; Str. viridans is found not infrequently, and occasionally hemolytic streptococci, staphylococci and other organisms may be isolated. Similarly the flora of the peritoneum following perforation of the bowel is rich and varied; it consists of aerobic and anaerobic organisms, gram-negative bacilli and gram-positive cocci of different types. Altemeier [5] has stated:

> Many avirulent strains of bacteria, particularly *B. coli*, become highly virulent in the presence of dead sterile tissue within the peritoneal cavity.
>
> In mixed culture these bacteria show a synergistic action producing a high degree of pathogenicity.

Thus fatal peritonitis can be caused by organisms not ordinarily considered to be virulent and pathogenic.

Numerous studies have been made of the inhibitory effect of both the readily absorbable and the relatively nonabsorbable sulfonamide compounds on the intestinal bacteria. Bliss and Long [6] showed the efficacy of sulfapyridine and sulfathiazole [7] and, to a lesser extent, of sulfanilamide in broth cultures of Esch. coli, Eberthella typhosa and beta hemolytic streptococci. Libby and Joyner [8] found sulfathiazole, sulfapyridine and sulfanilamide effective in vitro against the colon-typhoid-dysentery group of organisms. Lawrence [9] reported a significant reduction of the number of coliform organisms in mice fed with various sulfonamide compounds, although sulfanilamide proved ineffective.[7] Vieta and Stevenson [10] found that the coliform bacilli of the bowel were definitely reduced in 18 of 27 cases in which sulfadiazine was given. Firor and Jonas [11] and Stickney and colleagues [12] reported that sulfaguanidine produces an impressive reduction in the number of coliform organisms and a tendency toward a concomitant increase in Str. faecalis. Rodaniche and colleagues [13] confirmed and extended these observations. Broh-Kahn [14] concluded that the sulfonamide compounds act not only in an aerobic medium but also in an anaerobic one, an opinion shared by Clifton and Loewinger [15] but not by

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Fox and co-workers.[16] There can be no doubt, however, of the general inhibitory effect of the sulfonamide compounds on certain groups of bacteria. The sulfonamide compounds are given the credit by Ravdin and colleagues [17] for the lowering of the mortality rate of acute appendicitis from 1.5 per cent to 0.4 per cent.

With regard to the action of penicillin, Hobby and co-workers [18] found that the hemolytic streptococcus is twenty times more sensitive than the nonhemolytic Str. viridans. Herrell [19] noted that "Streptococcus faecalis, as well as many other strains of streptococci commonly referred to as green-producing (viridans) streptococci, is rather resistant to the action of penicillin." Dawson and colleagues [20] reported that Bay and Miller [21] have recently made a most interesting observation on a patient with bacterial endocarditis now well for more than three months after use of penicillin. Repeated blood cultures prior to therapy established the presence of an indifferent streptococcus. In vitro this organism grew out in time in a medium made up to contain 20 units of penicillin per cubic centimeter, an initial concentration probably greater than that present in the blood stream during therapy. These observations suggest the incompleteness of present knowledge concerning the effect of penicillin on certain gram-positive bacteria. It is generally agreed, however, that penicillin does not inhibit the growth of gram-negative bacilli.

Ungar [22] found that the inhibitory effect of penicillin in vitro is at least doubled by the presence of small quantities of sulfapyridine, insufficient per se to inhibit the growth of staphylococci or streptococci. Small doses of penicillin and of sulfapyridine, each inadequate to protect animals against these organisms, did protect when given together, suggesting the presence of a synergistic relationship between the two substances.

SUMMARY

In 3 cases of chronic ulcerative colitis with manifestations of generalized peritonitis recovery occurred; this was attributed primarily to therapy with sulfonamide compounds and penicillin, although blood transfusions and other supportive measures were used. In 1 patient two large abscesses were subsequently drained surgically. In another patient laparotomy three weeks later disclosed the loops of bowel bound together by the recent adhesions characteristic of peritonitis. In the third patient the clinical picture was typical of peritonitis, but no operation was performed. It seems that in general sulfonamide compounds tend to inhibit the growth of the gram-negative organisms in the bowel and penicillin that of the gram-positive ones. The possibility of a synergistic action of the two drugs also exists.

CONCLUSION

Combined sulfonamide and penicillin therapy is indicated in the treatment of peritonitis complicating nonspecific ulcerative colitis.

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SURGICAL THERAPY OF THE PATENT DUCTUS ARTERIOSUS

REPORT OF FIVE CASES

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A patent ductus arteriosus is a constant threat to life if allowed to persist. Bullock and colleagues [1] have collected 80 authenticated cases of death from untreated patent ductus arteriosus in patients over 3 years of age. Eleven (14 per cent) of the patients had died from their cardiac lesion by the age of 14; one half were dead by the age of 30, and 70 per cent by the age of 40. Two lived to the age of 66 years. The causes of death are listed in table 1. Although these statistics cannot be accepted unqualifiedly, they do indicate the seriousness of the condition. Ligation of the patent ductus arteriosus, a procedure which has been carried out with increasing frequency since Gross and Hubbard [2] reported the first case with successful results, in 1939, surgically corrects the defect and offers the chance of a normal life to thousands of patients suffering from this disabling and frequently fatal abnormality.

TABLE 1.—*Causes of Death in 80 Cases of Proved Patent Ductus Arteriosus Collected from the Literature by Bullock and Colleagues* [1]

	Deaths	
	Number	Per Cent
Bacterial endarteritis	42	53
Congestive failure	18	23
Rupture of the ductus and left ventricular failure	5	6
Associated cause of death	4	5
Death from other causes	6	7
Cause of death not given	5	6

DIAGNOSIS

The early diagnosis of uncomplicated patent ductus arteriosus is important and can be made in almost 100 per cent of the cases if the following criteria are present: (1) machinery murmur; (2) thrill in the pulmonary area; (3) enlarged pulmonary artery; (4) enlarged and pulsating pulmonary vessels; (5) enlarged heart; (6) increased pulse pressure; (7) stunting of growth; (8) absence of cyanosis and clubbing of fingers; (9) normal electrocardiogram, and (10) history of heart disease from early childhood. Not all these criteria may be present in every case. Their relative frequency as found by Shapiro [3] in 62 cases and by my colleagues and me in 5 cases is recorded in table 2.

The presence of a machinery murmur is listed by most observers as essential for diagnosis. Although in rare instances the diagnosis can be made without it, such diagnoses remain open to question until proved by autopsy or operation.

Occasionally other conditions, such as venous hum in infants and children, aortic regurgitation, interauricular and interventricular septal defects and other types of congenital defects, may be associated with or confused with patent ductus arteriosus. These, however, can usually be ruled out by the diagnostic criteria outlined previously.

TABLE 2.—*Relative Frequency of Criteria Necessary for Diagnosis of Uncomplicated Patent Ductus Arteriosus*

	Shapiro [3] (62 Cases)		Duke Hospital (5 Cases)	
	Present	Absent	Present	Absent
History of heart disease from early childhood	62	0	5	0
Absence of cyanosis and clubbing	62	0	5	0
Machinery murmur	61	1	5	0
Thrill in pulmonary area	53	9	4	1
Enlarged pulmonary artery	52	10	5	0
Normal electrocardiogram	52	10	3	2
Increased pulse pressure	48	14	2	3
Enlarged heart	40	22	1	4
Enlarged and pulsating pulmonary vessels	36	26	4	1
Stunting of growth	23	39	1	4

INDICATIONS FOR OPERATION

Surgical therapy is not applicable in all cases of patent ductus arteriosus. As a rule, only in

From the Department of Surgery, Duke University Hospital and School of Medicine.

1. Bullock, L. T.; Jones, J. C., and Dolley, F. S.: The Diagnosis and the Effects of Ligation of the Patent Ductus Arteriosus, J. Pediat. **15**:786-801 (Dec.) 1939.

2. Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus: First Successful Case, J. A. M. A. **112**:729-731 (Feb. 25) 1939.

3. Shapiro, M. J.: The Preoperative Diagnosis of Patent Ductus Arteriosus, J. A. M. A. **126**:934-937 (Dec. 9) 1944.

those cases in which the patent ductus is uncomplicated by other serious developmental defects is ligation suitable. Bullock and colleagues [1] have stated the belief, however, that if infants under 3 years of age and patients with cyanosis are excluded the probability that patent ductus arteriosus is associated with other significant anomalies is relatively small.

Is the diagnosis of uncomplicated patent ductus arteriosus indication enough for operation? Shapiro [3] has suggested that, since the operative results are not uniformly good, only the patients demonstrating evidence of cardiac strain or stunting of growth should undergo operation until more accurate statistical data on the effects of surgical treatment are available. His own statistics, however, clearly show that patients with this disorder rarely live beyond the age of 40, usually succumbing to congestive failure or bacterial endarteritis as a direct result of the patent ductus arteriosus. His analysis [4] of 140 cases in which operations were performed reveals 72 per cent with completely successful results, with an over-all operative mortality of less than 10 per cent. Contrast these results with the extremely high mortality from the disease itself if untreated, and the answer is clear. Similar objections have been raised by Burch,[5] who stated that the surgical risk is still not good enough in average hands to recommend operation for all patients with patent ductus arteriosus. He lists as indications for operation subacute bacterial endarteritis, definite cardiac decompensation, especially if progressive, and mental and physical retardation. The development of these complications is, of course, indication for therapeutic ligation. But should one wait for complications to appear before advising ligation merely because the operative risk is not good enough in average hands? Should one cease recommending gastrectomy for patients with intractable ulcer because the mortality is prohibitive in average hands? It is true that the relative newness of the procedure precludes its evaluation on a basis of long term postoperative follow-up observations. One may assume, however, that the conclusions drawn from studies on the ligation of large vessels elsewhere in the body apply as well to the ductus arteriosus. If permanent obliteration of the lumen of the ductus is obtained, recanalization is unlikely to occur. Thus, if no other defect exists, this otherwise irreversible condition can be reversed by surgical treatment and normal anatomic and physiologic relations restored. No long term follow-ups are necessary to attest this fact. From available evidence, therefore, prophylactic rather than therapeutic ligation appears to be the procedure of choice in competent hands.

4. Shapiro, M. J., and Keys, A.: The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention, Am. J. M. Sc. **206**:174-183 (Aug.) 1943.

5. Burch, G. E.: Congenital Patent Ductus Arteriosus; An Evaluation of Its Surgical Treatment, M. Clin. North America **28**:388-402 (March) 1944.

OPERATIVE TECHNIC

All methods employed to date, short of complete division of the ductus, are attended by a certain number of recurrences. Gross [2] first employed simple ligation with silk. This method has been employed successfully in 2 of our cases (case 1 and 2). In 14 such cases, however, Gross had several failures due to the reopening of the channel. In his next 28 cases, following principles laid down by Pearse [6] for the gradual occlusion of large vessels, he wrapped the ligated duct with cellophane, in the hope that the fibrosis promoted by the cellophane would cause permanent obliteration of the lumen in 100 per cent of cases. Even this method was followed by some failures. The technic had definite advantages over simple ligation, however, as was demonstrated by Harper and Robinson [7] in their case of infected patent ductus arteriosus. They noted immediate disappearance of the murmur after double ligation of the duct followed by loose wrapping with cellophane. The murmur reappeared two weeks after ligation but had faded within two months, and by two and a half months it had again disappeared and remained permanently abolished. This late ablation of the murmur they attributed to occlusion by the fibrosis set up by the cellophane. Dr. John Alexander [8] has suggested that the fibrosis from the cellophane might be so intense that the large vessels in apposition to it might become stenosed or paralysis of the recurrent nerve might ensue. Neither complication has been noted in any of the cases in which cellophane has been used.

Because of the failure attending any method of occlusion of large vessels by ligation in continuity, Gross [9] began dividing the ductus. This, of course, increases the hazards of operation and demands not only a skilled operator and

6. Pearse, H. E.: Experimental Studies on the Gradual Occlusion of Large Arteries, Ann. Surg. **112**: 923-937 (Nov.) 1940.

7. Harper, F. R., and Robinson, M. E.: Occlusion of Infected Patent Ductus Arteriosus with Cellophane, Am. J. Surg. **64**:294-296 (May) 1944.

8. Alexander, J., cited by Harper and Robinson.[7]

9. Gross, R. E.: Complete Surgical Division of the Patent Ductus Arteriosus: A Report of Fourteen Successful Cases, Surg., Gynec. & Obst. **78**:36-43 (Jan.) 1944.

perfect instruments but a skilled, experienced operating team.

It seemed to me that ligation of the duct with cellophane offered the safest and most efficient method of occlusion. Since the desired effect in ligation of the patent ductus arteriosus is immediate as well as permanent occlusion of the vessel, the technic recommended by Pearse for the gradual occlusion of large vessels by loosely wrapping them with cellophane does not necessarily apply. It was thought that perhaps an improvement in technic could be accomplished by combining the advantages of the broad ligature with the sclerosing action of the cellophane. To meet these requirements, a 25 cm. length of cotton tape was wrapped four times with cellophane held in place by sutures of fine cotton. This has been used successfully as a ligature in 3 cases (cases 3, 4 and 5). The technical details of the procedure are described in the case reports.

RESULTS

In 5 patients who have undergone operation at Duke Hospital, there have been no fatalities and no complications (table 3). All are considered clinically cured. In 1 case there was a superimposed bacterial endarteritis. Twenty-four hours after ligation of the infected ductus the cultures of the blood became sterile and have remained so for two years.

In 140 cases of operation collected from the literature by Shapiro and Keyes [4] (table 4), the mortality was less than 10 per cent, with 72 per cent considered completely successful. With

TABLE 3.—*Operative Results in Series from Duke Hospital*

Case	Age, Years	Sex *	Preoperative Complications	Post-operative Status	Length of Time Post-operative, Months
1	34	F	Bacterial endarteritis	Well	24
2	23	F	None	Well	2
3	14	F	Stunted growth	Well	4
4	21	F	None	Well	3
5	19	F	None	Well	1

* In all the cases in this series and in two thirds of those reported in the literature the disease occurred in women. The explanation of this phenomenon is unknown.

improvement in technic, I have every reason to believe that the over-all mortality will be less than 5 per cent. Of course, no method is perfect, and even with refinements in technic some failures must be expected. Ligation as a prophylactic measure, however, should prevent many complications incident to the persistently patent ductus. Some cardiologists now are loath to recommend operation, even in the presence of bacterial endarteritis, pointing to the recently reported "cures" obtained with penicillin in better than 50 per cent of patients suffering from bacterial endocarditis.[10] It should be remembered, however, that in patients with a patent ductus arteriosus and a superimposed bacterial

TABLE 4.—*Summary of Results of Surgical Intervention in Cases of Patent Ductus Arteriosus Collected from the Literature by Shapiro and Keys* [4]

Operations on patients without infection:		
Total number	107	
Completely successful	81	(76%)
Continuous murmur persists	14	
Rupture of duct at operation, with death	6	
Operation followed by bacterial endarteritis	2	
Infection of wound and mediastinitis	1	
Inoperable	1	
Vessel ligated not ductus arteriosus	3	
Error in diagnosis	2	
Operative deaths	9	(8.5%)
Operations on patients with bacterial endarteritis:		
Total number	33	
Completely successful	20	(60.6%)
Died at operation	5	(15.1%)
Persistent fever after successful ligation	8	
Total	140	
Total mortality	14	(10%)
Total completely successful	101	(72.1%)

infection, even if the blood stream is cleared of organisms, the predisposing factor remains and may again become the seat of infection. Penicillin therapy is, of course, invaluable as an adjunct to surgical treatment and certainly should be used in those few cases in which endarteritis develops in spite of or persists after ligation. It is unwise, though, to depend on penicillin alone in the treatment of the infected ductus.

SUMMARY AND CONCLUSIONS

In 5 cases of ligation of a patent ductus arteriosus with successful results occurring in women between the ages of 14 and 34 there was immediate abolition of the characteristic machinery murmur, with no recurrences in periods of observation from one to twenty-four months. Two patients had persistent systolic murmurs. One patient with a subacute bacterial endarteritis has been well for two years postoperatively. In 3 patients a cellophane-wrapped ligature has been used to occlude the ductus. No complications referable to the cellophane have been noted.

Prophylactic ligation of the uncomplicated patent ductus arteriosus by qualified surgeons

10. Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocardtis with Penicillin, J. A. M. A. **127**:129-137 (Jan. 20) 1945. Paullin, J. E., and McLoughlin, C. E.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, Ann. Int. Med. **22**:475-484 (April) 1945.

offers the possibility of a normal life expectancy to many patients who otherwise have little hope of living beyond the age of 40.

REPORT OF CASES

CASE 1.—C. W., a 34 year old married white woman, was admitted to Duke Hospital to Dr. Macdonald Dick's service April 27, 1943, complaining of fever and weakness of seven weeks' duration. A diagnosis of bacterial endocarditis had been made at her local hospital. She had failed to improve under therapy with sulfonamide drugs and was referred to Duke Hospital. Although in "excellent health" prior to the onset of her present illness, she had known since childhood that there was "something wrong" with her heart.

Physical examination revealed a thin, underweight woman with yellow skin (quinacrine hydrochloride). The temperature, pulse rate and respiration rate were within normal limits. No petechiae were visible. The heart was not enlarged. There was a pronounced thrill over the base in the second and third left intercostal spaces. In the same area a loud machinery murmur was audible. The blood pressure was 120 systolic and 60 diastolic. The remainder of the examination showed nothing abnormal.

Accessory clinical observations were: hemoglobin content 10.5 Gm. (68 per cent), erythrocyte count 3,580,000 and leukocyte count 8,600. Kahn and Kline tests of the blood elicited negative reactions. The results of urinalysis were normal. The electrocardiographic report stated that the record was slightly abnormal owing to changes in the T wave although the abnormalities were not striking.

Fluoroscopic and roentgenographic studies of the chest revealed prominent vascular hilar markings. The pulmonary conus was enlarged, and the pulsations were accentuated. The heart was not enlarged.

Four consecutive cultures of blood were positive for Streptococcus viridans (30 to 70 colonies per cubic centimeter).

A diagnosis of patent ductus arteriosus with superimposed bacterial endarteritis was made and ligation of the infected ductus advised.

Operation was performed on May 7 by Dr. Deryl Hart, using the technic recommended by Gross.[11] The ductus, measuring 2 cm. in diameter and 1 cm. in length, was ligated doubly with heavy braided silk.

Immediately after operation, her temperature, which had ranged from 99.5 to 102.5 F. preoperatively, returned to normal and did not rise above 99.5 F. during the remainder of her stay in the hospital. Her convalescence was entirely uneventful. Her blood, which on culture had yielded 30 colonies per cubic centimeter the day before operation, was sterile twenty-four hours after operation and remained sterile for six consecutive cultures. For the first three postoperative days slight hoarseness was noted, but this quickly cleared. Although the machinery murmur had disappeared after ligation, a rough systolic murmur persisted over the pulmonic area and was still audible on discharge one month after operation but had diminished in intensity. She received sulfadiazine for twelve days postoperatively.

On July 19 the patient returned for a check-up. The systolic murmur at the pulmonic area was still present. The blood pressure was 110 systolic and 70 diastolic. The blood was sterile on culture.

On December 20 the physical conditions were unchanged. The blood was sterile on culture, and the fluoroscopic abnormalities had reverted to almost normal.

CASE 2.—L. W., a 23 year old white single woman, was admitted to the hospital to Dr. Christopher Johnston's service April 3, 1945, complaining of having been "born with a leaking heart." She stated that she had always had a leaking heart and had never been able to run and play with other children because of the pronounced dyspnea and easy fatigability which she experienced. She was not incapacitated, however, until a year prior to her admission, when she began having attacks of severe stabbing pain over her heart and found that she could not walk over one-half block without becoming dyspneic.

Physical examination revealed a fairly well developed and nourished young single white woman with a normal pulse rate, temperature and respiration rate. Her blood pressure was 118 systolic and 68 diastolic. There was no cyanosis or clubbing of the extremities. The heart was slightly enlarged to the left. There was a pronounced thrill over the second and third left interspaces, with a definite systolic accentuation. A machinery murmur was audible also over the same area.

Accessory clinical observations were: hemoglobin content 80 per cent and leukocyte count 9,000. Kahn, Kline and Mazzini tests of the blood elicited negative reactions. The urine was normal. The electrocardiogram revealed slight left axis deviation. Fluoroscopic and roentgenographic examination of the chest showed the heart to be slightly enlarged to the left. The pulmonary artery was enlarged, with accentuation of its pulsation. No hilar dance was seen.

A diagnosis of uncomplicated patent ductus arteriosus was made, and on April 6, with the patient under endotracheally induced cyclopropane-ether anesthesia, a ductus, measuring 7 mm. in diameter and 12 mm. in length, was ligated by Dr. Deryl Hart, using essentially the same technic described in case 1.

Following ligation there was no significant change in blood pressure. The murmur disappeared after operation and was not heard again. Convalescence was uneventful, without a significant rise of temperature. The patient was out of bed on the tenth postoperative day and went home on the fourteenth.

CASE 3.—H. M. L., a 14 year old white girl, was first seen at Duke Hospital Sept. 9, 1941, complaining of frequent colds. During the course of her examination, a to and fro machinery murmur was heard in the third left intercostal space, and a diagnosis of patent ductus arteriosus was made. A tonsillectomy was performed on Sept. 19, 1942. She was not seen again until Nov. 12, 1944, when she was examined in the endocrine clinic for excessive and prolonged menarcheal bleeding and malnutrition. No recommendation was made at this time in regard to her patent ductus arteriosus. She returned to the hospital on Feb. 5, 1945, complaining of pain in the right lower quadrant of the abdomen. Her symptoms and signs were suggestive of appendicitis but cleared rapidly under observation. Because of the previous diagnosis of patent ductus arteriosus, the patient was questioned carefully in regard to symptoms referable to this lesion. She stated that she had always been small and underweight and had never been able to keep up with her playmates because of excessive fatigue and dyspnea on exercise. She had noted also pronounced dyspnea on climbing one flight of stairs. In recent months she had begun to have attacks of orthopnea. These facts were corroborated by her mother.

Physical examination revealed an extremely small, undernourished child appearing much younger than her

11. Gross, R. E.: Surgical Management of the Patent Ductus Arteriosus, Ann. Surg. **110**:321-356 (Sept.) 1939.

stated age. The temperature, pulse rate and respiration rate were within normal limits. There was a continuous thrill with systolic accentuation in the second and third interspaces on the left, most pronounced in the second. A machinery murmur was audible in the same areas. The heart was not enlarged. The blood pressure was 112 systolic and 40 diastolic. The liver was palpable just below the costal margin. The remainder of the examination was noncontributory.

The accessory clinical observations were: hemoglobin content 12.2 Gm. (79 per cent) and leukocyte count 9,720; Kahn, Kline and Mazzini tests of the blood elicited negative reactions. The results of urinalysis were normal. The electrocardiogram was normal. Fluoroscopic examination and roentgenograms of the chest showed an exceedingly active pulsation throughout, especially of the left ventricle and the aorta. The pulmonary conus was prominent and active.

In summary, this patient presented all the diagnostic criteria for patent ductus arteriosus as outlined by Shapiro except an enlarged heart.

The parents were advised of the seriousness of the condition and readily consented to operation.

On February 12 operation was performed with the patient under endotracheally induced cyclopropane-ether anesthesia. With the patient supine and the left arm extended above the head, a curved left submammary incision was made, the pectoral muscles severed at their attachments to the thorax and the breast and muscles reflected upward. The left pleural cavity was entered through the third intercostal space and the second and third costal cartilages divided near the sternum. A rib spreader was inserted and the lung packed off with warm moist pads. Excellent exposure of the lateral aspect of the superior mediastinum was obtained. An

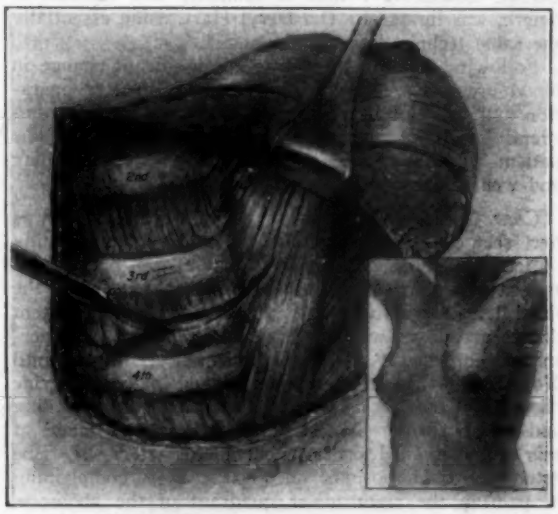

Fig. 1.—The incision used for exposure of the ductus.

incision was made in the pleura between the phrenic and vagus nerves and carried well up over the arch of the aorta. The vagus nerve was readily identified and followed down to the point at which the recurrent nerve curved back under the arch of the aorta. Palpation of this area revealed a pronounced thrill which could be abolished on pressure. The ductus, located readily by these measures, was carefully cleaned off by gently pushing aside the surrounding fat. A large channel, approximately 2 cm. in diameter and 5 mm. in length, was found connecting the aorta and pulmonary artery. After it had been completely isolated and a curved clamp passed behind it, a 25 cm. length of cotton tape which had been wrapped four times with cellophane held in place by fine cotton sutures was grasped in the clamp and pulled under it. A single tie was placed in the ligature and tightened sufficiently to abolish the thrill. The excess cellophane was then stripped from the tape down to the knot, to decrease the bulk of the ligature,

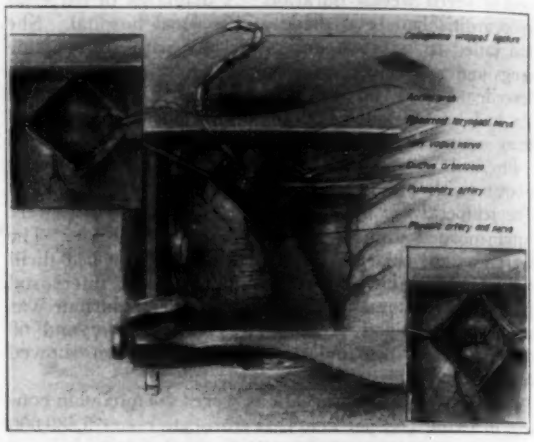

Fig. 2.—Chest open. The left upper inset shows the incision in the mediastinal pleura below the phrenic nerve and over the arch of the aorta. The relation of the ductus and the vagus and recurrent nerves can be seen. The central figure shows the clamp which has been passed behind the ductus grasping the cellophane-wrapped ligature preparatory to pulling it through. The lower inset shows the ligature in place.

and a square knot placed over the first tie. After the duct had been ligated, it was thought that the thrill had not been completely abolished and an additional braided silk tie was placed about the duct. This "thrill" later was found to originate in the bronchial tree. No sudden change in pulse pressure was noted after ligation of the ductus, although there had been a steady decrease apparent from the time manipulation and digital compression of the duct had begun. During the course of the ligation, it was necessary to exercise extreme care to avoid injury to the recurrent nerve. The pleura overlying the vessels was closed with interrupted fine cotton sutures. The wound was then closed by pulling the ribs together with stay sutures of no. 2 chromic surgical gut, reattaching the pectoral muscles with interrupted sutures of medium cotton and closing the subcutaneous tissue and skin with interrupted fine cotton. During the course of the operation the patient received a transfusion of 500 cc. of blood and at the close of the procedure appeared in excellent condition.

The convalescence was uneventful. There was an immediate postoperative rise in temperature to 101.6 F., which promptly fell to normal in forty-eight hours. She received sulfadiazine and penicillin prophylactically for several days postoperatively. She was out of bed on the fourth day and went home on the thirteenth postoperative day. The machinery murmur, which had been audible preoperatively, completely disappeared after ligation and did not reappear while she was under observation. On discharge her blood pressure was recorded as 110 systolic and 68 diastolic, there was a decrease in pulse pressure of 30 mm. of mercury.

On May 18 the patient returned for a routine check-up. She had no complaints except occasional twinges of pain under the incision where the costal cartilages had been divided at operation. She had been feeling well and gaining weight. She no longer experienced dyspnea on climbing stairs and had had no orthopnea.

Examination revealed a well healed operative scar. No murmur was audible. Blood pressure in both arms was 110 systolic and 74 diastolic. Fluoroscopic examination and roentgenograms of the chest showed a decrease in size and pulsation of the pulmonary conus.

Case 4.—N. H. D., a 20 year old white woman, was first admitted to the hospital on May 2, 1944, complaining of weakness, loss of weight and brown discoloration of the face of two months' duration. She gave no history of frank cardiac failure but admitted exertional dyspnea in excess of normal and occasional attacks of orthopnea. All her life she had been easily fatigued and had been unable to keep up with her playmates. She had also noticed some edema of the ankles. There was no history of chills or fever.

On examination the patient appeared well nourished and normally developed. There were splotchy brownish areas of discoloration over the face, neck and extremities. No thrill was present, but a loud machinery murmur with systolic accentuation was audible in the third left intercostal space. The heart was not enlarged. The blood pressure was 112 systolic and 60 diastolic. The remainder of the examination was essentially noncontributory.

The accessory clinical observations were: hemoglobin content 13.2 Gm. (85 per cent), erythrocyte count 4,050,000 and leukocyte count 6,160. The results of urinalysis were normal. Kahn, Kline and Mazzini tests of the blood elicited negative reactions. Electrocardiographic tracings were normal. Roentgenologic examination of the chest showed no evidence of cardiac enlargement, but the pulmonary conus was definitely prominent. Accentuation of the pulsations of the left ventricle, the aorta and the pulmonary vessels was noted.

A diagnosis of patent ductus arteriosus and chloasma was made. The patient and her family were advised of the dangers of a persistently patent ductus arteriosus, and ligation was advised. Operation was refused, and the patient left the hospital on May 17.

She returned on Feb. 20, 1945, stating that she wished to have the operation which had been advised nine months earlier, since her husband and her local physician had strongly urged her to have it.

The physical conditions were essentially unchanged. The murmur was still clearly audible, but no thrill was present. No additional observations were recorded.

The accessory clinical observations were identical with those of the previous admission.

On February 20, with the patient under endotracheally induced cyclopropane-ether anesthesia, the ductus was ligated, the technic described in case 3 being used. The duct in this case was smaller than that in the preceding case, measuring only 8 to 10 mm. in diameter and 12 to 15 mm. in length. The blood pressure changed suddenly at the time of ligation from 124 systolic and 74 diastolic to 124 systolic and 88 diastolic. The systolic pressure later fell to 110, but the diastolic pressure was maintained at 90.

Immediately after ligation the murmur disappeared and was not heard again during an uneventful convalescence. The temperature showed a slight rise to 101.1 F. on the second postoperative day but by the fourth day had returned to normal, where it remained without further variation. She received penicillin prophylactically for several days postoperatively. She was out of bed on the eighth day and went home on the eleventh day. On discharge her blood pressure was recorded as 100 systolic and 70 diastolic; there was a decrease in pulse pressure of 22 mm.

The patient returned to the clinic for her regular postoperative examination six weeks after operation. At that time she had no complaints. She volunteered the information that she no longer noted the excessive fatigue and exertional dyspnea described before operation. She wanted to return to her old job in the mill. Examination revealed no thrills or murmurs. The blood pressure was 120 systolic and 60 diastolic.

Case 5.—K. M. G., a 19 year old white married woman, was first treated at Duke Hospital March 4, 1939 for acute sinusitis. While in the hospital, a thrill and a to and fro machinery murmur were found in the second and third left interspaces. Albumin, red cells and casts were found in her urine. A diagnosis of a patent ductus arteriosus and chronic glomerulonephritis was made and conservative treatment initiated. The patient was readmitted twice during the following six weeks for her sinusitis, and an ethmoidectomy and a submucous resection were done. She was not seen again at this hospital until March 30, 1945, when she was examined in the gynecology clinic regarding sterility. The only abnormalities found were retroversion of the uterus and chronic cervicitis. Conservative treatment for these conditions was recommended. She was sent to the medical clinic for evaluation of her cardiac status. Because of the presence of a persistently patent ductus arteriosus, she was admitted to the surgical service on May 7 for consideration of ligation. A careful history was taken with regard to symptoms referable to her patent ductus arteriosus, and the following facts were elicited: She was unaware that there was anything wrong with her heart until approximately eleven years previously, when her local physician, during the course of a routine examination, found that she had a "leaking of her heart." Although she had never been able to keep up with other children because of excessive fatigability and dyspnea, she was not seriously bothered with the condition until several years prior to her present admission, when these symptoms became more pronounced.

Physical examination revealed a fairly well developed and nourished pale young white woman with a normal temperature, pulse rate and respiration rate. There was no cyanosis or clubbing of the extremities and no petechiae. The heart was not enlarged. There was a thrill over the second and third interspaces on the left with a systolic accentuation. A machinery murmur, also with systolic accentuation, was noticed over the same areas. A very soft apical systolic murmur was present. The blood pressure was 110 systolic and 70 diastolic in the left arm and 114 systolic and 70 diastolic in the right. The remainder of the physical examination was noncontributory.

Accessory clinical observations were: hemoglobin content 13.3 Gm. (86 per cent), erythrocyte count 4,590,000 and leukocyte count 9,080. Kahn, Kline and Mazzini tests of the blood elicited negative reactions. The blood nonprotein nitrogen level was 27 mg. per hundred cubic centimeters. Urinalysis showed nothing abnormal. A phenolsulfonphthalein test showed normal excretion of the dye. The electrocardiographic report was not indicative of myocardial disease. Fluoroscopic and roentgenographic examination of the chest revealed the lungs to be clear except for a moderate increase of vascular markings throughout both pulmonary fields. The pulmonary artery was prominent, with increased

pulsation. The heart was otherwise normal, with no enlargement. There was no definite hilar dance.

On May 10, with the patient under endotracheally induced cyclopropane-ether anesthesia, operation was performed by Dr. David Wilson, using the technic described in case 3. The ductus, which measured approximately 7 to 8 mm. in diameter and 5 mm. in length, was ligated doubly instead of singly with the cellophane-wrapped ligatures. After ligation, the blood pressure, which had been stabilized at 140 systolic and 80 diastolic, changed to 140 systolic and 100 diastolic.

After operation the temperature rose to 100.7 F. on the third day and returned to normal on the eighth day. The patient felt well, and no cause could be found for this slight persistent elevation of temperature. She received penicillin and sulfacetamide prophylactically. On the sixth day a few red cells were found in her urine. Because of her history of glomerulonephritis, studies of renal function were carried out. There was rather poor concentration after dehydration, but the urea clearance was normal. A very faint systolic murmur was heard in the second left interspace on the sixth day. The murmur was not constant and disappeared on inspiration. The machinery murmur had completely disappeared, however. She was discharged on the twelfth day, with her wound well healed.

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ULCERATING LESIONS OF THE GASTROENTERIC STOMA

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Innumerable studies have been made on the subject of gastrojejunal ulcer. The majority of them, however, have been concerned principally with the diagnosis and treatment of the condition, and little has been written on the pathologic findings. We are presenting the pathologic as well as the clinical features of gastrojejunal ulcer in 100 cases in which tissue showing the gastroenteric stoma and the ulcer was available. In all 100 cases, the specimens had been removed between 1932 and 1944. Two blocks were cut from each of the 100 specimens, and the sections made from these blocks were stained with hematoxylin and eosin. One block was made through the anastomotic junction extending through the ulcer, unless the size of the ulcer prohibited. The other section was made through that portion of the anastomotic ring in which no gross ulceration was present.

REVIEW OF LITERATURE

Walton [1] in 1934 concluded on the basis of his own studies and others that the incidence of gastrojejunal ulcer following gastroenterostomy for duodenal ulcer is probably 3 to 4 per cent, and Judd and Hoerner [2] in 1935 reported an incidence of 2.8 per cent. Balfour [3] in 1917 reported 100 cases of gastric ulcer in which gastroenterostomy was performed and in which no gastrojejunal ulceration ensued. No recurrent ulceration was reported by Walters and Clagett [4] in 252 cases of gastric ulcer treated by gastroenterostomy. However, in 1935, Wright,[5] in reporting the results in 884 cases of gastric ulcer in which gastroenterostomy was performed, found that gastrojejunal ulcers developed subsequently in about 10 per cent of the cases. Balfour [6] and Benedict [7] stated that gastrojejunal ulcer is a disease of men. Most investigators are generally agreed that the highest incidence is in the age period between 30 and 50 years, although they seem to believe that gastrojejunal ulceration can occur at almost any age.

Pathology of Gastrojejunal Ulcer.—In 1927 Heidbreder [8] reported on the pathologic changes of gastrojejunal ulcer. He stated that the mucosa appeared hypertrophic and inflamed and contained many goblet cells filled with mucus. Edema was noted between the mucosa and the muscularis mucosae. Lymphocytes were found scattered here and there in the stroma of the villi. Apparently most of the thickening as seen in gross sections at the site of the stomas was due to an increase in the connective tissue elements. The nonulcerating intestine was only half as thick as the ulcer-involved intestine. In healthy tissue, the mucosa occupied half of the thickness of the wall and the serosa was found in close relation to the muscularis propria. In the portion of the intestine in which the ulcer had developed, however, the mucosa was atrophied, the stroma of the villi was filled with lymphocytes, the submucosa showed some lymph follicles and a dense

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* From the Section on Surgical Pathology, Mayo Clinic.

This paper is an abridgment of a thesis submitted by Dr. Tosseland to the faculty of the University of Minnesota Graduate School in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

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2. Judd, E. S., and Hoerner, M. T.: Jejunal Ulcer, Ann. Surg. **102**:1003-1018 (Dec.) 1935.

3. Balfour, D. C.: Results of Surgical Treatment of Gastric Ulcer, Surg., Gynec. & Obst. **24**:731-736 (June) 1917.

4. Walters, W., and Clagett, O. T.: The Surgical Treatment of Chronic Gastric Ulcer: Review of 272 Cases, Surg., Gynec. & Obst. **71**:75-79 (July) 1940.

5. Wright, G.: Collective Inquiry by the Fellows of the Association of Surgeons into Gastrojejunal Ulceration, Brit. J. Surg. **22**:433-455 (Jan.) 1935.

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8. Heidbreder, W.: Klinische und histologische Untersuchungen zur Frage der peptischen Jejunalgeschwüre bei vorderer Gastroenterostomie und Braunscher Anastomose, Arch. f. klin. Chir. **146**:685-700, 1927.

accumulation of connective tissue cells in the muscularis propria separated it from the serosal layer.

Nemiloff [9] in 1925 presented the histologic observations from a study of the tissue at the site of 8 gastroenteric stomas. In 6 cases gastroenterostomy had been performed for duodenal ulcer and in 2 for carcinoma of the pylorus of the stomach. Seven of the stomas examined were obtained at necropsy, performed from two to twenty-four days after gastroenterostomy. Death had been from causes unrelated to the stoma in all 7 cases. In the eighth case, the stoma was obtained nine months after the original gastroenterostomy, at an operation performed for gastrojejunal ulcer.

Nemiloff stated that healing of the wound at the site of the gastroenterostomy was by secondary intention. Severe inflammatory and degenerative changes were noted in all the various coats of the stomach, but the most severe changes were seen in the mucosa. The mucosa in the region of the anastomosis was almost entirely absent down to its deepest layers soon after gastroenterostomy, and only a few isolated glands were left from which regeneration could take place. Apparently regeneration began at about the twelfth to fourteenth day, but the defect in the junction of the mucosal layers was still present in a specimen obtained twenty-four days after gastroenterostomy. In the remaining coats of the stomach and intestine, especially in the muscle layer, partial degeneration was found at the anastomotic junction; in the muscle layer no regeneration occurred at the line of junction except through connective tissue. Silk sutures seemingly caused rather severe and long-continuing inflammation and slowing of healing but evidently became cast off into the lumen of the stoma after a period of weeks. The healing process evidently did not effect complete restoration of normal structures, because in many cases the appearance of the submucosa was abnormal, the muscularis mucosae was absent and the muscularis propria was replaced by scar tissue in places or interwoven with strands of connective tissue, with no evidence of true regeneration of the muscle tissue.

Angerer [10] in 1927 made a study of tissue near three stomas secured at secondary operations two, five and "a number of" years following the original gastroenterostomy. He found that the muscularis mucosae in his specimens was absent at and near the line of junction and that the submucosa was absent or replaced by connective tissue. The muscularis propria was distorted, and the union was effected mainly by connective tissue. On the jejunal side of the anastomosis, he found what he concluded were islands of pyloric glands with cystic dilatation. These, he decided, were the result of metaplasia. Rosenow and one of us (J. R. M.)[11] in 1943 pointed out that these glands could well be Brunner's glands in the jejunum. In a later section of this paper, this observation will be verified.

In the American literature, the work of Archer [12] in 1939 on the histology and histopathology of the gastroenteric stoma is significant.

Smyth [13] found that the ulcer was rarely more than 1 inch (2.5 cm.) from the stoma. It was usually located in the distal loop but was sometimes found on the mesenteric border of the jejunum directly opposite the stoma. He listed the types of ulcers as acute, subacute and chronic. The latter two tend to resemble the usual picture of a peptic ulcer with slight variations.

Estes [14] in 1932 reported, on the other hand, that the ulcer is found most often in the line of the anastomosis but may occur in the jejunum within 2 to 3 cm. of the anastomosis. In the latter location it has a great tendency to perforate. He further stated that the ulcer may involve only a small portion of the stoma or its entire lumen with extensive infiltration of the adjacent mesocolon and may partly or completely close the stoma. Such an ulcer may perforate into the colon to form a gastrojejunocolic fistula.

Walton [1] described two types of ulcer: the acute gastrojejunal ulcer and the chronic ulcer of long standing. He concluded that all ulcers begin at the anastomotic line, because he found scarred tissue extending from the stoma to the ulcer in all instances.

9. Nemiloff, A.: Ueber den Heilungsprozess in der Gastroenterostomiewunde, Arch. f. klin. Chir. **135**:629-639, 1925.

10. Angerer, H.: Zur Histologie alter Gastroenterostomiestellen und deren Umgebung, Deutsche Ztschr. f. Chir. **201**:228-242 (March) 1927.

11. Rosenow, J. H., and McDonald, J. R.: The Histology and Histopathology of the Gastro-Enteric Stoma, with Especial Reference to Gastrojejunitis, Gastroenterology **2**:161-179 (March) 1944.

12. Archer, G. F.: Histopathology of Old Anastomotic Wounds Involving the Stomach and Jejunum, Thesis, Graduate School of the University of Minnesota, 1939.

13. Smyth, M. J.: Gastro-Jejunal Ulcer, Irish J. M. Sc., October 1931, pp. 553-563.

14. Estes, W. L., Jr.: Advanced Gastrojejunal Ulcer, Ann. Surg. **96**:250-257 (Aug.) 1932.

It is apparent from the studies of Lindau and Wulff,[15] Johnston and Renner[16] and Cobb[17] that the ulcers seen in Meckel's diverticulum are similar to gastrojejunal ulcers. About the only significant difference is the fact that the ulcers of Meckel's diverticulum occur primarily in childhood and gastrojejunal ulcers occur in middle age. This difference can be explained adequately on the basis that Meckel's diverticulum is a congenital anomaly whereas the gastrojejunal ulcer is the handiwork of the surgeon.

Symptoms.—Estes in 1932 described the predominant symptom as being pain one to one and a half hours after eating. This pain was similar to or more severe than the original ulcer pain and located to the left of the midline of the epigastrium, with tenderness at this point on palpation. Benedict described the symptoms of gastrojejunal ulcer as being pain, hematemesis and melena. He found that the pain was usually lower than the original pain and to the left of the umbilicus and sometimes extended to the left groin. Apparently this pain was not a predominant symptom after a fistula was established.

Walton reported that there were two definite groups of cases clinically. In the first, hematemesis is a predominant symptom, and in the second, and more common, variety, he found that in the earlier stages there were mild degrees of discomfort and flatulence. This was replaced later by definite pain simulating that from the original lesion, the attacks of pain being periodic but more severe than that from the original lesion and frequently awakening the patient at night. The pain, he found, was referred to the lower part of the abdomen and especially to the left iliac fossa. Vomiting was found to occur frequently and usually gave transient relief from the pain.

According to Wright, pain was the cardinal symptom in his series of 458 cases.

Walters and Clagett[18] in 1939 stated that a gnawing hunger type of pain came on between meals and occasionally awakened the patient at night. The pain could be relieved by food or alkalis but was not as easily controlled as the distress of the original lesion. Although the pain could be epigastric, it frequently shifted below and to the left of the site of the original distress.

Rivers and Gardner[19] in 1940 concluded that the symptoms were similar to those produced by the original lesion but that gastrojejunal lesions were more penetrating, caused more constant distress and more distress at night and were less easily relieved by food and alkali. They mentioned that obstruction may distort the ulcer syndrome but that if there are no complications these lesions send pain along the splanchnic nerves as visceral phenomena. Pain of a perforating ulcer caused true stimulation of the spinal sensory nerves with referred pain along the distribution of the sensory nerves.

PRESENT INVESTIGATION

Age.—It was found in our study of 100 cases that gastrojejunal ulcer is a disease of middle age. The ages of the majority of patients (81) ranged from 30 to 59 years. The range of ages of the 100 patients was from 19 to 73 years. These figures compare favorably with the results of other investigations.

Sex.—Duodenal ulcer has been shown to be primarily a disease of men. Since most of the gastrojejunal ulcers in the cases herein studied followed operative procedures aimed to cure or relieve patients suffering from duodenal ulcers, it can be assumed that gastrojejunal ulcer should occur more often in men than in women. In the present study, 93 of the patients were men and 7 were women.

Symptoms.—Pain was the most common symptom of gastrojejunal ulcer in our patients. Pain of one sort or another was present in 86 per cent. Although pain was rather constantly encountered, its location varied greatly. In some the original pain produced by duodenal ulcer, which was usually in the epigastrium, occurred; in others the pain extended downward to either the right or the left side of the umbilicus or upward to the shoulder blades, as does the pain from cholecystic disease. At times the pain extended downward as far as the groin. This shifting of pain downward from its original site was described by 55 per cent of the 86 patients in whom pain was present and was not mentioned

15. Lindau, A., and Wulff, H.: Peptic Genesis of Gastric and Duodenal Ulcer, Especially in Light of Ulcers in Meckel's Diverticulum and Postoperative Ulcers in Jejunum, Surg., Gynec. & Obst. **53**:621-634 (Nov.) 1931.

16. Johnston, L. B., and Renner, G., Jr.: Peptic Ulcer of Meckel's Diverticulum: A Report of Two Cases and a Review of the Literature, Surg., Gynec. & Obst. **59**:198-209 (Aug.) 1934.

17. Cobb, D. B.: Meckel's Diverticulum with Peptic Ulcer, Ann. Surg. **103**:747-764 (May) 1936.

18. Walters, W., and Clagett, O. T.: Gastrojejunal Ulcer: A Study of One Hundred and Fifty-Five Cases, Am. J. Surg. **46**:83-93 (Oct.) 1939.

19. Rivers, A. B., and Gardner, J. W.: Recurrent Peptic Ulcer: Situation of Recurrences and the Importance of Studies of Pain in the Recognition of Such Recurrences, J. A. M. A. **115**:1779-1785 (Nov. 23) 1940.

by 45 per cent. Surprisingly, in only 17 per cent of the cases in this series did the patients have pain at night severe enough to awaken them from sleep.

In general, the patients considered that the pain of gastrojejunal ulcer was more severe, more constant and less relieved by the taking of milk, alkali or food than was the pain of duodenal ulcer. In most of the cases rather extensive attempts at medical management to relieve symptoms had been tried and failed before surgical intervention was attempted.

Hemorrhage was the next most common symptom, and this, of course, is a complication as well. In 32 per cent of the cases hematemesis and melena occurred. In 42 per cent melena alone occurred. Hemorrhage varied from the massive single hemorrhages which immediately endangered the patient's life to the repeated smaller hemorrhages which sapped his strength and caused anemic states.

Vomiting occurred in 24 per cent of the cases. In some instances it almost directly followed meals and was spontaneous. Vomiting of this type apparently caused relief of distress, and it is assumed that it indicated an obstruction to the outflow of the stomach's contents. In other instances the vomiting was self induced and gave relief from distress. In these cases, however, the distress usually occurred an hour or more after meals. This self-induced vomiting may represent obstruction, but other factors may be present.

Pathology and Histopathology.—From all practical standpoints, gastrojejunal ulcers may well be called anastomotic or stomal ulcers. However, the histologic examination in our cases showed that 81 per cent of the ulcers were on the jejunal side of the anastomosis; 3 per cent, on the gastric side, and 3 per cent, on the anastomotic line, and the site of 13 per cent could not be determined. The sections in the indeterminate group showed jejunal mucosa on one side of the ulcer, but in preparation the mucosa had been torn away from the opposite side. In those cases in which the junction could be demonstrated, the distance from the ulcer to the stoma ranged from 2 to 13 mm. in the fixed specimen. This is less than it would be in life, owing to the shrinkage that accompanies the preserving process (figs. 1, 2 and 3).

In general, the ulcers resembled the peptic ulcers described in the literature. They had the typical rounded, stamped-out appearance of peptic ulcers. The mucosa and submucosa were absent over the base of the ulcer; the muscular layers were completely replaced by fibrous tissue, and the serosa was absent in all instances. It is probable, however, that the absence of the serosa was the result of preparation of the slide.

Study of the anastomotic junction revealed that the mucosa was well united in most instances. The mucosa at the junction usually varied somewhat from the normal. Parietal cells were seen in the gastric mucosa adjacent to the anastomosis in the majority of cases. Frequently the jejunal mucosa ended abruptly, and the gastric mucosa joined it directly. In other instances, jejunal glands might be seen on the gastric side of the anastomosis, but they were always within a short distance of the anastomosis. Gastric glands with acid cells were seen as frequently on the jejunal side of the anastomosis. The submucosa was infiltrated by connective tissue at the line of junction; the muscularis mucosae was interrupted at the junction, and the muscularis propria was united by connective tissue at the anastomotic line.

As was pointed out by Rosenow and one of us (J. R. M.), Brunner's glands can occur and are found in the jejunum. Of the sections through the ulcer in this series, 6 per cent revealed typical Brunner's glands (fig. 4), whereas 18 per cent of the sections made through the line of anastomosis away from the ulcer revealed these glands.

Simple cysts were present in 22 per cent of the microscopic preparations which showed the ulcer and in 17 per cent of microscopic preparations which showed the junction only (fig. 5*a*). Rosenow and one of us (J. R. M.) pointed out that these cysts could originate either from pyloric glands or from Brunner's glands. It is not possible on the basis of this study to state the origin of the cysts except in 1 instance, in which the mucosal lining of the cyst was definitely jejunal epithelium with typical goblet cells. The cysts usually occurred near the anastomoses.

In the majority of cases a moderate or a severe degree of both gastritis and jejunitis was noted. Part of this reaction was undoubtedly a result of the ulceration.

Since suture material is considered the etiologic agent in one of the older theories of the production of ulcer, the sections were reviewed in an attempt to ascertain the presence of suture material and suture reaction. Five per cent of the histologic sections through the ulcer and 9 per cent of the sections through the anastomosis re-

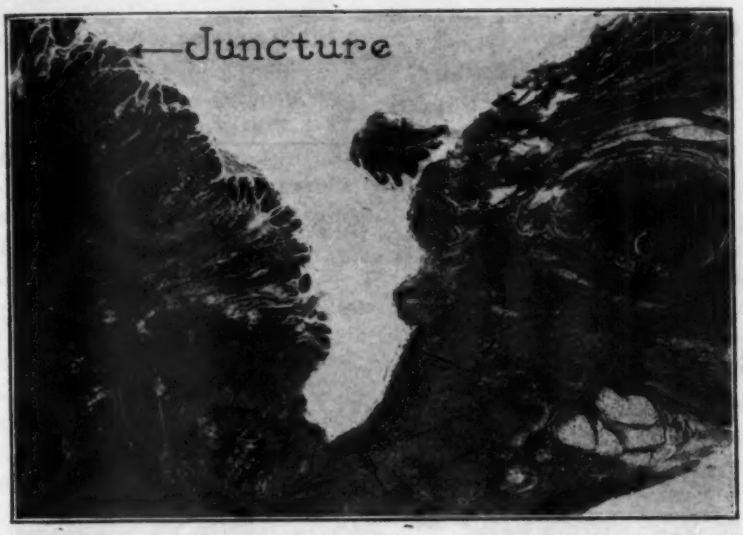

Fig. 1.—Typical burrowing ulcer on the jejunal side of the stoma. The gastric mucosa is located to the left of the juncture (× 6½).

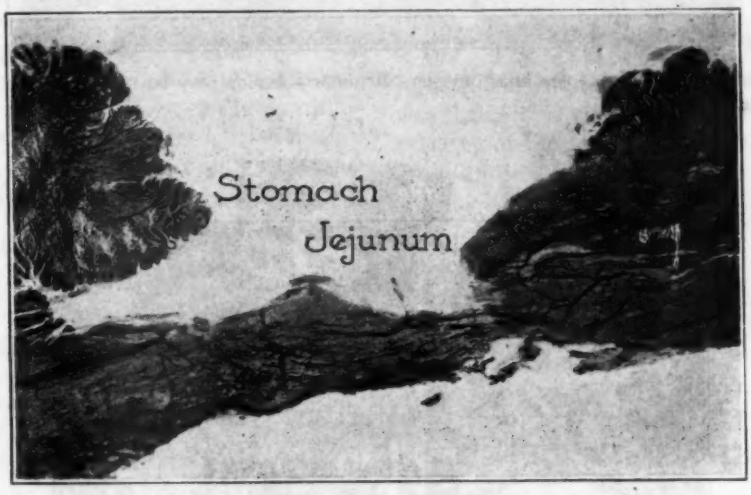

Fig. 2.—Ulcer on the anastomotic line (× 10).

Fig. 3.—Ulcer on the gastric side of the anastomosis (× 12).

Fig. 4.—Ulcer on jejunal side of the anastomosis. Brunner's glands may be noted beneath the jejunal mucosa on the left side of the ulcer (× 12).

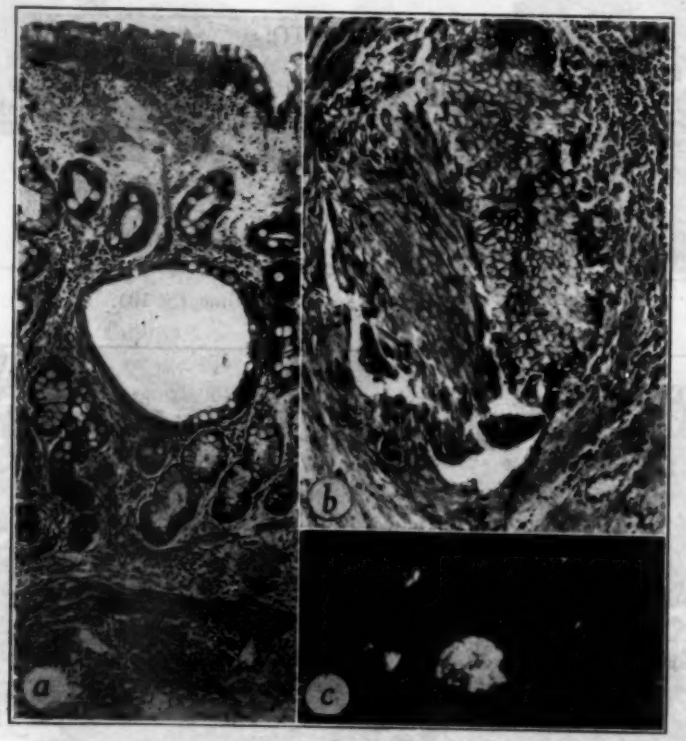

Fig. 5.—(*a*) Simple cyst of the jejunum near a gastrojejunal anastomosis (× 70); (*b*) suture material and the reaction to it at site of the gastrojejunal junction (× 90); (*c*) magnesium silicate as seen under polarized light (× 165).

vealed such a process (fig. 5 *b*). In view of these low figures, it is probably safe to assume that suture material does not play the significant role it was thought to play in the production of ulcer.

Magnesium silicate, such as is found in talc, also has been considered a foreign body capable of producing inflammatory changes and probably ulcers. The histologic preparations were examined under the polarizing microscope, and identification of the crystals was made according to the method described by Ramsey.[20] In approximately 8 per cent, magnesium silicate was found (fig. 5 *c*). Although this percentage is not large and certainly cannot be considered enough evidence for any conclusions concerning the role of magnesium silicate in the production of ulcer, the possibility that talc may be an etiologic factor should not be entirely overlooked. The obvious source of this foreign body is the talc (U. S. P.) used on surgeons' gloves.

The cases were reviewed in an attempt to correlate the severity of clinical symptoms with the pathologic changes, but little correlation was evident. In some instances of severe gastrojejunitis only mild symptoms occurred, whereas, on the other hand, in some cases of mild gastrojejunitis clinical symptoms were rather severe.

20. Ramsey, T. L.: Magnesium Silicate Granuloma, Am. J. Clin. Path. **12**:553-558 (Nov.) 1942.

SUMMARY

The incidence of ulceration following gastroenterostomy for duodenal ulcer has been reported in the literature as varying from about 2 to 4 per cent. In general, the incidence reported in the literature for ulceration following gastroenterostomy for gastric ulcer is much less. In the present study, a detailed clinical and pathologic study was done in 100 cases in which resection of the stomach was carried out for gastrojejunal ulcer. Parietal cells were seen in the gastric mucosa adjacent to the gastric enteric stoma in the majority of these cases. In 81 of the 87 cases in which it was possible to determine the site of ulceration in relation to the anastomotic line, the ulcer occurred on the jejunal side, in 3 on the gastric side and in 3 on the anastomotic line. Simple epithelial cysts were found at or near the anastomotic line in approximately 1 in 5 cases. Brunner's glands were found occasionally in the jejunal mucosa adjacent to the stoma. The majority of cases showed gastrojejunitis of moderate or severe degree. There was little or no correlation between the degree of severity of the symptoms and the degree of gastrojejunitis. Suture material and magnesium silicate were found in the region of the gastroenteric stoma but appeared to have little direct relationship to the ulcer.

LEIOMYOSARCOMA OF THE UTERUS WITH METASTASIS TO THE FEMUR

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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Sarcoma of the uterus was first described by Virchow in 1860. Since then, many isolated cases and collected series of cases have been reported. In most cases the sarcoma is discovered unexpectedly as a result of removing a fibroid tumor, and thus these cases are usually reported as a percentage of cases of uterine fibroids examined pathologically.

Opinion differs as to whether malignant myomas are malignant from the beginning or whether they represent a malignant change in an originally benign tumor. Ewing [1] said that these tumors are malignant from the start. Masson [2] took a different viewpoint and felt that they may originate in fibromyomas or in adjacent connective, muscle or endometrial tissue.

The reported incidence of uterine sarcoma varies from 0.2 to 10 per cent, with the majority of observers favoring an incidence of 0.5 to 2 per cent. Vogt [3] collected reports of 72,116 cases of myoma from the literature and found the average incidence of sarcoma to be 0.4 per cent. The rarity of the condition was commented on by Ewing [1]; he had seen but 3 malignant uterine myomas with general metastases and 2 with local recurrence in twenty years.

Histologically, the more common forms of sarcoma of the uterus are the spindle cell, the round cell (large or small), the giant cell and the mixed cell types. Of these, the spindle cell sarcoma is seen most often. As a group, sarcomas grow more rapidly than carcinomas. Fibrosarcomas and myosarcomas, the types usually found in the uterus, metastasize later than other sarcomas, since they are comparatively solid growths. The small round cell sarcoma is the most malignant type and is more apt to be fatal, because of early metastases.

Most observers have felt that the number of mitotic figures present is in direct proportion to the malignancy of the tumor. Evans [4] graded these sarcomas by counting the mitotic figures in 1 cu. mm. of tumor. He considered group I, with 2,200 to 12,000 mitoses per cubic millimeter, to be highly malignant; group II, with 200 to 800, to be borderline, and group III, with 0 to a few, to be premalignant.

Masson [2] stated that malignant tumors found in the uteri of infants and young children are almost always sarcomas. During menstrual life malignant tumors are more often cancerous, and after the menopause sarcomas are again relatively more common. The highest incidence of uterine sarcoma is in the fifth and sixth decades.

It is the general opinion that distant metastases are rare. The incidence of bony metastases of malignant leiomyoma, regardless of the primary site, is even rarer. Ewing [1] stated that malignant myoma metastasizes to liver, lungs, kidneys, peritoneum and lymph nodes but made no mention of metastases to bone. Willis,[5] in his book "The Spread of Tumours in the Human Body," said nothing about the spread of uterine sarcoma to bone.

Decio,[6] in 1939, reported a case of uterine sarcoma with metastasis to the humerus. Robbins,[7] in 1943, reported a case of sarcoma of the uterus with roentgenologic evidence of spinal metastasis occurring three years after removal of the primary tumor and a second case with roentgenologic evidence of metastasis to the spine one year after

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1. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 226-228.

2. Masson, J. C.: Sarcoma of the Uterus, Am. J. Obst. & Gynec. **5**:345-357, 1923.

3. Vogt, M. E.: Sarcoma of the Uterus, with a Report of Thirty Cases, Am. J. Obst. & Gynec. **5**:523-529, 1923.

4. Evans, N.: Malignant Myomata and Related Tumors of the Uterus, Surg., Gynec. & Obst. **30**:225-239, 1920.

5. Willis, R. A.: The Spread of Tumours in the Human Body, London, J. & A. Churchill, Ltd., 1933, p. 413.

6. Decio, C.: Humeral Metastases of Uterine Sarcoma: Case, Riv. ital. di ginec. **22**:640-646, 1939.

7. Robbins, L. L.: Roentgenologic Demonstration of Spinal Metastases from Leiomyosarcoma of Uterus, Arch. Surg. **47**:463-467 (Nov.) 1943.

removal of the primary tumor. The diagnosis in both of these cases was proved at autopsy. Blackman [8] had a case in which a tumor of the skull was excised two years after the uterus had been removed for what was thought to be multiple myomas. This tumor proved to be a smooth muscle neoplasm. These are the only reported cases which we have been able to find in which bony metastases occurred from a leiomyosarcoma of the uterus. Our attention was brought to the subject by a case which we thought sufficiently interesting to be reported.

Fig. 1.—July 1943. Except over the greater trochanter, the cortex of the left femur appears intact. There is noticeable rarefaction in the upper end of the shaft of the femur and in the head and neck of the bone.

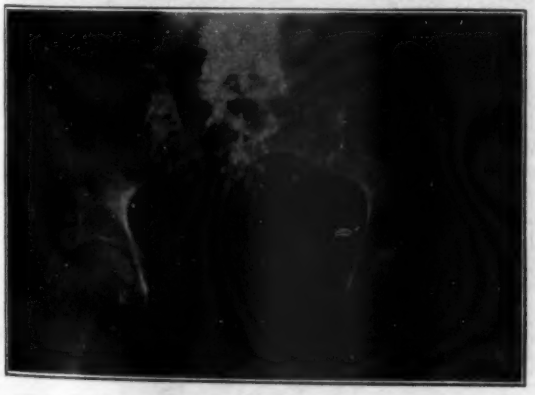

Fig. 2.—March 1944. This film shows the femur as it was on admission of the patient to the hospital. There is a fracture of the neck of the femur with definite upward displacement of the shaft, showing extensive destruction of the bone and an increase in rarefaction of the head of the femur over that shown in figure 1.

8. Blackman, S.: Personal communication to the authors.

REPORT OF CASE

A. H., a white woman aged 43, was admitted to Salt Lake County General Hospital on March 17, 1944, complaining of pain in the left hip of eight weeks' duration.

In September 1939, in another hospital, an operative diagnosis of myomas of the uterus had been made. Symptoms leading to operation were menorrhagia which had been present for one and one-half years and a continuous profuse vaginal bleeding for a month. A subtotal hysterectomy was done with unilateral salpingectomy and bilateral partial oophorectomy. The pathologist's report was multiple fibromyomas of the uterus, malignant degeneration (myosarcoma) of a submucous fibroma and lutein cyst of an ovary. We have examined these sections. They show a spindle cell sarcoma with a few mitotic figures. After the operation, the patient had irregular menstrual periods at intervals of twenty days to two months with minimal bleeding lasting one to two days.

Fig. 3.—May 1944. Appearance of the left femur after traction had been applied. There is a decided increase in rarefaction in the upper part of the shaft of the femur. The head shows spotty erosive areas with a prominent increase in density around the periphery.

In July 1943, while employed as a secretary, the patient began to have pain in the left knee when she stood or walked though there was no pain when at rest. She consulted a physician, who made roentgenograms of the left knee and hip. These films (fig. 1) show an abnormal process consisting of diffuse erosion of the head of the femur, especially in the neck. The bony contours are normal, but there are many small translucent areas in the bone. The patient failed to return to the physician but consulted a chiropractor for treatment of the pain in the hip. This pain continued in about the same intensity until the morning of Jan. 15, 1944, when she was unable to get out of bed

Fig. 4.—June 1, 1944. Further destruction of bone has occurred. A fracture of the head fragment is now present.

because of severe pain in the left hip. She was admitted to another hospital, at which roentgenologic examination showed a fracture of the neck of the left femur which was thought to be pathologic. Her left leg was placed in a hip spica plaster cast, and she was sent to a nursing home; from there she was admitted to this hospital eight weeks after the fracture occurred.

Physical Examination.—The patient was an extremely obese white woman. Moderate diffuse enlargement of the thyroid was noted. No masses were palpable in the breasts. The heart and lungs were normal. The left leg was in a spica cast, along the edges of which there were numerous pressure ulcers. Vaginal examination, though unsatisfactory owing to the cast, revealed no fixation of the pelvic structures and no abnormal masses.

Laboratory Data and Roentgenologic Observations.—The hemoglobin content of the blood was 12.75 Gm., and there were 7,450 white cells. Urinalysis revealed no abnormalities. The blood calcium level was 8.6 mg. per hundred cubic centimeters; the phosphorus level,

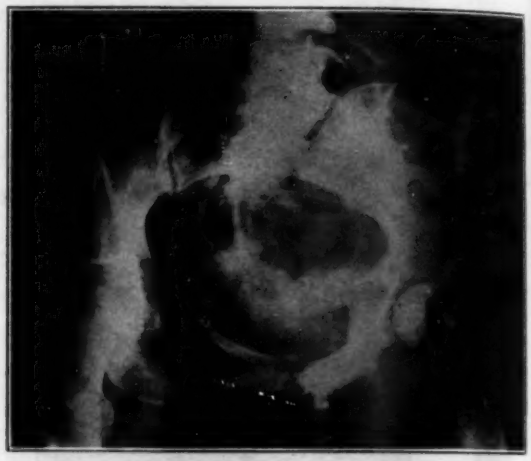

Fig. 5.—June 22, 1944. Progressive destruction of the head and upper part of the shaft of the femur. The neck has been destroyed by the invasive myoma.

5.58 mg., and the alkaline phosphatase activity, 4.9 units. Serologic tests of the blood gave negative results, and the reaction to tuberculin (purified protein derivative) was negative.

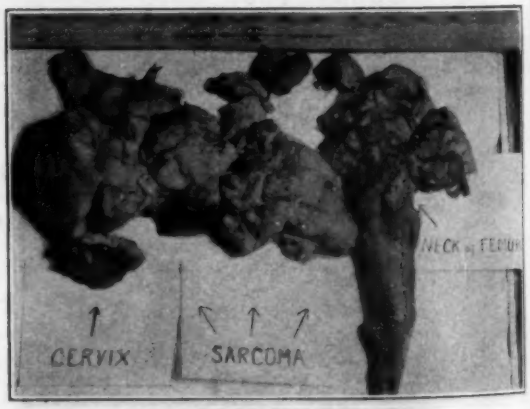

Fig. 6.—Gross specimen, as removed at autopsy, showing the cervix, with the tumor tissue surrounding and invading it, and the tumor, as it extended out to the left femur. The erosive destruction of the upper part of the shaft of the femur with the tumor tissue attached to the bone is seen. The eroded fragments of the head of the femur are seen at the top.

A roentgenogram of the chest and intravenous pyelograms showed normal conditions. Films of the left hip (fig. 2, March 22) show a fracture involving the neck of the left femur, with distinct upward displacement of the lower fragment and some apparent erosion

and rarefaction of the neck of the femur. This was definitely thought to be due to a pathologic fracture resulting from bony metastasis.

Course.—A biopsy of the femur at the fracture site was made on March 28. Microscopic sections showed interlacing bundles of spindle-shaped cells resembling smooth muscle cells and little intercellular substance. mitotic figures were observed, and these were atypical forms.

The biopsy wound became infected, and there were an associated fever and leukocytosis. Culture of material from the wound grew beta hemolytic Staphylococcus aureus. Local irrigations and sulfamerazine by parenteral injection were given, without improvement.

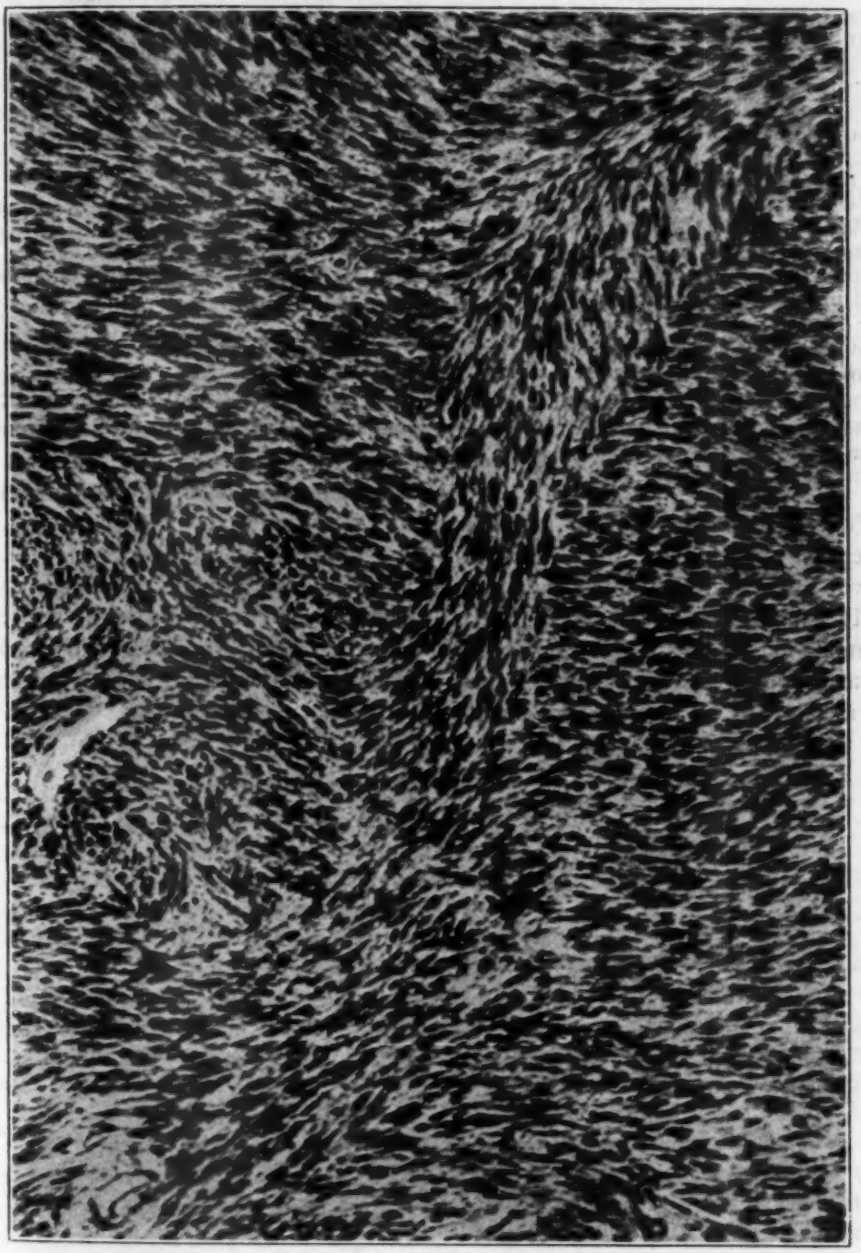

Fig. 7.—Low power photomicrograph of a section taken from the tumor involving the femur. Notice the interlacing bundles of spindle-shaped cells and the variation in shape and in density of staining of the nuclei.

There was palisading of the nuclei. In the entire section, the tissue was more cellular and less uniform in structure than in the ordinary benign leiomyoma. The nuclei in many areas showed inequality in size and variation in shape and in density of staining. Irregular pyknotic masses of nuclear substance were observed in large numbers, but comparatively few clearly defined

Subsequent roentgenologic examinations of the region of the left hip showed (figs. 3, 4 and 5) progressive damage and destruction of the head and neck of the left femur. Additional films of the chest showed no evidence of pulmonary metastases.

The patient's course continued to be septic; she rapidly lost weight; a large severe decubitus ulcer

developed over the sacrum, and the infection in the biopsy wound spread. She died July 8.

Clinical Impression.—The clinical observations were: (1) pathologic fracture of the neck of the left femur due to metastasis of a leiomyosarcoma of the uterus; (2) severe decubitus ulcer, and (3) infected biopsy wound.

Autopsy.—Permission for local and regional examination only was obtained. A large, grayish white, moderately firm mass of tissue was found in the region of the upper part of the shaft of the left femur; it involved the surrounding muscles and extended into the obturator foramen as far as the hand could reach. The upper part of the shaft and the head and neck of the femur were removed with the tumor substance en bloc (fig. 6). Through a small midline abdominal incision, this whitish tumor mass could be felt in the pelvis, extending up along the spine to the upper part of the abdomen. The cervix was removed through the vagina, and its vaginal surface and abdominal surface were observed to be involved with tumor.

Microscopic sections from the cervix, the abdominal tumor mass and the left femur (fig. 7) showed a spindle cell leiomyosarcoma.

Anatomic Diagnosis.—The diagnosis was leiomyosarcoma of the uterus with extension to the pelvis, abdomen and left femur.

CONCLUSIONS

Sarcoma of the uterus is a rare neoplasm, probably occurring in not more than 1 per cent of patients who are operated on for uterine fibromyomas. Metastases from sarcoma of the uterus are most common in the lungs, peritoneum, lymph nodes, liver and kidneys. Little has been written concerning metastases of uterine sarcomas to bone. We were able to find only 3 cases reported, and we know of 1 questionable case through personal communication.

In the case reported the neoplasm does not conform with Evans'[4] classification of uterine sarcomas as to their degree of malignancy according to the number of mitotic figures present. Our case would fall, according to his classification, in the cases of group III sarcomas, showing only a few mitotic figures, but the course of the patient proved the malignancy of the tumor.

SUMMARY

1. Sarcoma of the uterus is a relatively uncommon disease.

2. The condition may be encountered in children, but it is more common in women in the postmenopausal period, especially during the fifth and sixth decades.

3. It is not certain whether the tumor arises primarily or whether it develops from a preexisting fibroid.

4. The number of mitotic figures is usually an index to the degree of malignancy.

5. Distant metastases are rare. Only 3 cases in which there were metastases to bone have been found reported in the literature.

6. A fourth proved case, in which metastasis occurred in the femur, is reported here.

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